Performance Improvement Measures: Breast Cancer Survivorship

Measure 1: Bone health assessment, screening and management among breast cancer patients receiving adjuvant endocrine therapy or experiencing premature ovarian failure

Measure 1a: Percentage of patients who were assessed for osteoporosis risk

Measure 1b: Percentage of patients identified in (1a) as having elevated risk of osteoporosis who received a baseline bone density scan and follow-up scans if sufficient time has passed

Measure 1c: Percentage of patients identified in (1a) who received appropriate therapies and lifestyle counseling

Patients included in measure:
- women
- known or assumed first or only cancer diagnosis
- primary tumors of the breast, stages I-III
- receiving endocrine therapy or experiencing ovarian failure secondary to treatment
- known to be alive within 24 months of diagnosis

Evidence:
NCCN Practice Guidelines for Breast Cancer, v.1.2009, recommends that:
“Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter.” Use of a bisphosphonate is the preferred intervention to improve bone mineral density and current clinical evidence supports use of a bisphosphonate for up to 2 years.¹

ASCO guidelines: “Breast cancer patients found to have osteoporosis based on BMD results (t score -2.5 or lower) should have pharmacologic therapy initiated with an agent demonstrated to have efficacy.”²
Measure 2: Assessment and appropriate intervention for menopausal symptoms among women receiving adjuvant endocrine therapy or experiencing premature ovarian failure

Measure 1a: Percentage of patients who were asked about menopausal symptoms

Measure 1b: Percentage of patients with menopausal symptoms who received counseling and/or therapeutic interventions and/or referral to mental health professionals as determined on an individual basis

Patients included in measure:
- women
- known or assumed first or only cancer diagnosis
- primary tumors of the breast, stages I-III
- receiving endocrine therapy or experiencing ovarian failure secondary to treatment
- known to be alive within 24 months of diagnosis

All patients should be asked about symptoms and all should receive counseling.

Evidence:
Guidelines in this area are still evolving. The Institute of Medicine’s 2005 report “From Cancer Patient to Cancer Survivor: Lost in Transition” identifies intervention for consequences of cancer and its treatment, including sexual dysfunction, as an essential component of survivorship care. The NCCN Practice Guidelines in Oncology on Distress Management, v.1. 2011 recommend that patients with cancer be screened for sexual problems and referred for counseling if needed. ASCO guidelines on hormone deficiency states and sexual dysfunction in female cancer survivors are pending.
Measure 3: Assessment of risk of future infertility, interest in future fertility, and among those interested in fertility and at risk of infertility, counseling and referral as appropriate for fertility preservation counseling and intervention.

**Measure 3a:** Percentage of patients who were asked about their interest in future fertility prior to treatment

**Measure 3b:** Percentage of patients who were advised/counseled regarding risk of infertility with treatment prior to treatment

**Measure 3c:** Percentage of patients who were counseled and/or referred for consideration of fertility preservation options

Patients included in measure:
- women
- known or assumed first or only cancer diagnosis
- primary tumors of the breast, stages I-III
- age 45 or younger (childbearing age)
- known to be alive within 24 months of diagnosis

All premenopausal women should be counseled about the risk of amenorrhea and permanent menopause with chemotherapy.

**Evidence:**
Current ASCO guidelines recommend that all women of childbearing age be advised of their risk of infertility, assessed for their interest in future fertility, and referred or counseled regarding fertility preservation options prior to treatment.5
Measure 4: Assessment of physical activity, counseling regarding rationale for and optimal physical activity levels after breast cancer and how to improve physical activity in breast cancer survivors.

Measure 4a: Percentage of patients who were asked about their level of physical activity.

Measure 4b: Percentage of patients who were advised/counseled regarding the potential benefits of exercise after breast cancer.

Measure 4c: Percentage of patients who were counseled regarding increasing or maintaining exercise level, and/or counseled or referred for assistance to help increase physical activity.

Patients included in measure:
- women
- known or assumed first or only cancer diagnosis
- primary tumors of the breast, stages I-III
- known to be alive within 24 months of diagnosis

Evidence:
This performance measure is based on a wide range of evidence for the benefits of exercise to all individuals as well as breast cancer survivors. Although exercise is not a part of the most recent NCCN guidelines on breast cancer, it is recommended as part of their general advice to cancer patients. Exercise is also listed as an intervention in the NCCN guidelines for distress management in cancer patients. Recent studies that have examined the benefits of exercise specifically in breast cancer patients include a randomized controlled trial showing that strength training reduced risk factors for fracture among postmenopausal breast cancer survivors. A recent systematic review of randomized controlled trials on exercise in breast cancer concluded that aerobic exercise performed with or without weight training is a common feature of exercise programs that report significant quality of life-related outcomes. The most commonly reported exercise parameters were three sessions per week, at moderate intensity being equivalent to 50% to 80% of the maximum heart rate for greater than 30 minutes.
References:

American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer

By Bruce E. Hillner, James N. Ingle, Rowan T. Chlebowski, Julie Gralow, Gary C. Yee, Nora A. Janjan, Jane A. Cauley, Brent A. Blumenstein, Kathy S. Albain, Allan Lipton, and Susan Brown

Purpose: To update the 2000 ASCO guidelines on the role of bisphosphonates in women with breast cancer and address the subject of bone health in these women.

Results: For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended. The presence or absence of bone pain should not be a factor in initiating bisphosphonates.

In patients with a serum creatinine less than 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval is required. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. Creatinine should be monitored before each dose of either agent in accordance with US Food and Drug Administration (FDA) labeling.

Conclusions: Bisphosphonates provide a supportive, albeit expensive and non-life-prolonging, benefit to many patients with bone metastases. Current research is focusing on bisphosphonates as adjuvant therapy. Although new data addressing when to stop therapy, alternative doses or schedules for administration, and how to best coordinate bisphosphonates with other palliative therapies are needed, they are not currently being investigated.

THE AMERICAN Society of Clinical Oncology (ASCO) publishes evidence-based clinical practice guidelines. As part of the process, the expert panel reviews and updates the guidelines on a regular basis. This document represents an update of the guideline for the use of bisphosphonates in breast cancer that was published in 2000. The use of bisphosphonates in other solid tumors may be the subject of future ASCO clinical practice guidelines.

For the 2003 update, the Panel (see appendix) reviewed the published data since 2000. Computerized Medline searches were performed, meeting abstracts were reviewed, and members of the industry were contacted and given the opportunity to provide data. In preparing this update, it was decided that the related subject of bone health was important to consider. Although the initial impetus for this decision was the increasing utilization of nonsteroidal aromatase inhibitors, it is clear that the importance of bone health is not restricted to women receiving these agents. The ASCO Board of Directors approved this expansion in the scope of the guideline in November 2002.

The Panel had two meetings to consider the evidence for each of the 2000 recommendations. The guideline was circulated in draft form to the full expert panel and to the ASCO Health Services Committee for review and approval. The document was then reviewed and approved by the ASCO Board of Directors. Each recommendation from the 2000 guidelines is listed below, and is followed by an updated (2003) recommendation, if applicable. “No change” is indicated if a particular recommendation has not been revised. A summary of the evidence follows thereafter.

ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances. It cannot be assumed that these guidelines apply to interventions performed in clinical trials, which are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that guideline development involves a review and synthesis of the latest literature, and a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

Background

Since the publication of the 2000 guidelines on bisphosphonates in breast cancer, a variety of events have occurred that...
prompted this current update. Among these events is the approval of a new intravenous bisphosphonate, zoledronic acid, for use in women with breast cancer. Although discussed in the 2000 guidelines, clodronate continues to be available in the United States only as an investigational therapy. A new drug application to the US Food and Drug Administration (FDA) for clodronate has, to date, never been submitted. The potential renal toxicity of intravenous pamidronate and zoledronic acid has prompted specific recommended monitoring schedules by the FDA. The interest in assessing bisphosphonates as adjuvant therapy has expanded. Since 2000, two randomized clinical trials using oral clodronate as an adjuvant therapy have been reported. These issues will be subsequently discussed.

Although the Panel reviewed numerous publications on the subject since 2000, the vast majority of reports were reviews revisiting the small current collection of clinical trials. Since 2000, no major randomized controlled trials in the metastatic setting have been initiated. Therefore, it is unlikely that in the foreseeable future there will be any new data addressing the issues of when to start, stop, alternative dose, or schedule bisphosphonates. While some have criticized the original guidelines for recommending ‘the extensive and early use of bisphosphonates’, there have been no efforts to systematically address the outstanding questions. The interest of the major clinical trial groups in the US, Canada, and Europe has shifted to the adjuvant setting. Several different trials have been, or are expected to be, initiated.

GUIDELINES FOR THE USE OF BISPHOSPHONATES IN BREAST CANCER

In these guidelines, recommendations about the indications for using bisphosphonates for bone disease in breast cancer are presented in the context of three clinical presentation scenarios for patients with breast cancer. These include women with imaging evidence of bone metastases, women with extra-skeletal metastases without evidence of bone metastases, and bisphosphonates as adjuvant therapy.

BISPHOSPHONATE USE IN WOMEN WITH IMAGING EVIDENCE OF BONE METASTASES

Lytic Disease on Plain Radiographs

2000 recommendation. Intravenous pamidronate 90 mg delivered over 1 to 2 hours every 3 to 4 weeks is recommended in women with metastatic breast cancer who have plain radiograph(s) that show lytic destruction of bone and who are receiving systemic therapy with hormonal therapy or chemotherapy.

2003 recommendation. For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status and overall prognosis.

Evidence Summary

The Panel based its revised recommendation on reviewing all of the available literature but specifically focused its critical appraisal on the single randomized comparison of zoledronic acid to pamidronate. A detailed comparison of the entry criteria, design, statistical planning and reporting, and results is listed in the 2002 ASCO multiple myeloma guidelines. In addition, the guidelines were modified to indicate that the duration of infusion of pamidronate should be 2 hours rather than a shorter duration. The basis for this decision is related to the potential for renal toxicity as discussed in the section on safety and adverse events.

Pamidronate. There are no new randomized placebo controlled trials evaluating the use of intravenous pamidronate. Pamidronate was used as the control in the randomized comparison to zoledronic acid (discussed below). There are no new data addressing the optimal dose, duration, or dosing interval. There is new information on safety issues, specifically renal toxicities, discussed later.

Clodronate. There are no new reports of clodronate in the metastatic disease setting.

Zoledronic acid. In February 2002, the FDA approved an expanded indication for zoledronic acid that included its use in metastatic breast cancer and multiple myeloma (www.fda.gov/cder/cancer). This new indication is based on a large randomized comparison to pamidronate.

Two randomized trials showed that zoledronic acid can be given safely over a short interval and produce similar antiresorptive effects as administering 90 mg of pamidronate, as assessed by bone resorption markers. The first randomized phase II study, compared this newer bisphosphonate to pamidronate in 280 patients with lytic bone metastases from either myeloma (n = 108) or breast cancer (n = 172). Patients were randomly assigned to nine monthly infusions of 0.4 mg, 2.0 mg, or 4.0 mg zoledronic acid in a 5-minute infusion, or to 90 mg pamidronate as a 2-hour infusion. The primary end point was to determine a dose(s) of zoledronic acid that reduced the need for radiation to less than 30% of treated women, although all skeletal related events (SREs) were also evaluated as in the previously reported pamidronate trials. SREs were an aggregate of all sites and number of pathologic fractures, spinal cord collapse/compres,

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creatinine that occurred more frequently among patients receiving zoledronic acid, the infusion time for zoledronic acid was increased from 5 minutes to 15 minutes during the trial. Despite this change, renal problems occurred more often among patients randomly assigned to 8 mg zoledronic acid, and as a result, the dose was reduced to 4 mg.

The trial’s sample size was based on showing equivalence (noninferiority), not superiority, of zoledronic acid to pamidronate. Noninferiority was concluded if the observed difference was less than the upper limit of difference in the one-sided 95% CI in SRES between zoledronic acid and pamidronate—a difference of 8%. The trial’s sample size was sufficient to have an 80% power using a one-sided significance of 0.05. The trial included 1,130 patients with metastatic breast cancer who were evaluated in the intent to treat analysis approximately every 3 months for 13 months. Secondary end points of pain and performance status showed similar effects to those in prior studies. Details related to pain were not reported other than to say that 53% of patients had a pain score greater than zero at the beginning of the study and 69% had a decrease in their pain scores. The average decline in pain score was about 0.5 on a five-point scale. Analgesic use and Eastern Cooperative Oncology Group (ECOG) performance status over the 13 months were ‘fairly stable’.

In all treatment groups, about 50% of patients reported an adverse event; however, less than 5% of those events were classified as drug-related. Seven percent of patients discontinued therapy because of an adverse effect. The frequency of serious renal-related adverse events was 1.9% in the higher dose (8 mg) zoledronic acid group compared with 0.5% in the 4 mg zoledronic acid group and 0.2% in the pamidronate group. After modifying the infusion schedule of zoledronic acid, it appears that the incidence of renal impairment declined, but the number of patients was small. Novartis (East Hanover, NJ) provided additional follow-up data for the panel regarding the breast cancer patients in this trial. At 25 months, there was no difference in the proportion of patients having a SRE (46% to 48% with zoledronic acid vs 49% with pamidronate). The median survival rate was also no different at ~25 months.

Subset analyses that were not preplanned found that patients initially treated with hormonal therapy and zoledronic acid compared with pamidronate needed less radiation therapy to the bone (0.33 events/yr v 0.58 events/yr; P = .015). This needs to be prospectively confirmed before its importance in guiding decision-making can be assessed.

Cook and Major7 have recently highlighted that bone complications, especially fractures, may not be independent events but rather ones that occur in clusters. One advocated method to the statistical evaluation of these type of data is a multiple-event analysis. Furthermore, it is important to keep in mind that the results from analyses using multiple event models need to be subjected to careful demonstrations of the stability of the conclusions when assumptions are varied.

Analyses based on multiple event data must be interpreted with care, especially in contrast to results using more straightforward analyses. Each of the commonly used statistical methods for multiple event analyses require more assumptions about the nature of the data and also require making somewhat arbitrary decisions about how to represent events in the analysis. The results from analyses using multiple event models need to be subjected to careful demonstrations of the stability of the conclusions when assumptions are varied.

**Other guidelines.** Several other groups or individuals have addressed the role of bisphosphonates in breast cancer. The Cochrane Breast Cancer Review Group has recently completed an extensive literature review of previously reported randomized trials evaluating bisphosphonates.8 This review identified 19 randomized trials. In their analysis of eight studies involving 1,962 women with advanced breast cancer and existing bone metastases, bisphosphonates reduced the risk of developing a skeletal event by 14% (95% CI; risk ratio [RR], 0.80 to 0.91). For intravenous pamidronate, the reduction in the risk of skeletal event using a 90 mg dosage was 23% (95% CI; RR, 0.73 to 0.94) and for oral clodronate was 16% (95% CI; RR, 0.72 to 0.98; P = .03). Compared with placebo, bisphosphonates reduced the skeletal event rate by a median of 30% overall (range, 20% to 48%). They concluded, based on the single study discussed above, that zoledronic acid appeared to have equivalent efficacy when compared with intravenous pamidronate.

Another recent review addressed the role of oral bisphosphonates in myeloma and breast cancer and concluded that oral bisphosphonates do not appear to be as effective as those administered intravenously.9

In December 2002, Cancer Care Ontario updated its guidelines on the use of bisphosphonates in women with breast cancer (www.cancercare.on.ca/ccopgi).8 Their guidelines recommend that women with breast cancer who have bone metastases should be offered treatment with oral clodronate or intravenous pamidronate. Intravenous zoledronic acid was considered an alternative to pamidronate when a shorter infusion time (15 minutes) is “important”. No examples were given to guide providers in determining “importance”. The remainder of the Cancer Care Ontario guidelines on the role of bisphosphonates in the adjuvant setting, pain control, and the absence of data on the optimal duration of therapy, agree with what is later discussed in this update.

**Panel deliberations.** Although the conclusions of the Cochrane Breast Cancer Group review suggest that both clodronate and pamidronate are likely to be superior to placebo, the judgment of the Panel was that the recommendation be made only for the use of intravenous pamidronate and zoledronic acid. Reasons for this recommendation include: (1) clodronate has not yet been approved for use in the U.S.; (2) the evidence for clodronate was clouded by the potential for an overestimation of its effect, based on the use of events per person per year; and (3) the inability to aggregate all the relevant skeletal end points. A review of the zoledronic acid/pamidronate protocol by the Panel confirmed that this multiple event assessment was one of at least seven preplanned secondary efficacy analyses of the comparative...
trial. Multiple event analyses are statistically more complex, may be subject to after-the-fact assumptions, and ideally, should be independently validated. The Panel concluded that there was insufficient evidence to conclude that the effectiveness of zoledronic acid was superior to pamidronate. The publication of the full multiple event analysis report of this trial is awaited with interest.

**Abnormal Bone Scan, Normal Radiographs but Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) Scan Showing Bone Destruction**

**2000 recommendation.** Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction and localized pain, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with osteolytic changes on plain radiographs.

**2003 recommendation.** Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs.

**Abnormal Bone Scan, Normal Radiographs, and No Evidence of Bone Destruction on CT or MRI**

**2000 recommendation.** Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, tomograms, CT scans, or MRI, or with localized pain, is not suggested.

**2003 recommendation.** Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.

**SAFETY AND ADVERSE EFFECTS**

**2003 Recommendation.** In patients with pre-existing renal disease and a serum creatinine level less than 3.0 mg/dL (265 µmol/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly, even though there is no evidence on which to base a recommendation for time intervals. In contrast to multiple myeloma patients, there currently is no data to support routine assessments for albuminuria in breast cancer patients.

**Evidence Summary**

Short-term use of bisphosphonates, when administered according to recommended infusion doses, infusion times, and dosing intervals, is associated with a low risk of renal dysfunction. In a randomized comparison of pamidronate (90 mg as a 2-hour infusion) versus zoledronic acid (4 mg as a 15-minute infusion),6 6% to 8% of patients with breast cancer experienced deterioration of renal function during the first 12 months of bisphosphonate therapy. In that study, deterioration of renal function was defined as change in baseline serum creatinine ≥ 0.5 mg/dL or ≥ 2 times baseline value in patients with normal baseline serum creatinine (<1.4 mg/dL), or a change from baseline serum creatinine ≥ 1.0 mg/dL, or ≥ 2 times baseline value in patients with abnormal baseline serum creatinine (≥1.4 mg/dL). One of 365 patients in that trial developed grade 3 renal toxicity, according to the National Cancer Institute Common Toxicity Criteria (Personal communication, Hei YJ, Seaman J, Novartis Pharmaceuticals, 2003).

There are limited data on the long-term renal safety of bisphosphonates. In an uncontrolled study of 22 patients treated with pamidronate (n = 18) or zoledronic acid (n = 4) for more than 2 years (median, 3.6 years), the last serum creatinine level was significantly higher than baseline values.10 Although shorter infusion times may be tolerated on a short-term basis, shorter infusion times have been associated with a higher risk of renal toxicity. Intravenous infusions of pamidronate over less than 2 hours, especially those ≤ 1 hour given on a long-term basis (> 1 year), have been occasionally associated with renal toxicity including albuminuria followed by azotemia. More serious renal toxicity has also been reported with long-term use of higher doses or more frequent dosing of pamidronate.11-13 Most cases occurred among patients with multiple myeloma, although some also occurred among patients with breast cancer. The kidney pathology may show a collapsing focal segmental glomerulosclerosis12,13 or tubulointerstitial nephritis.11 Recently, several case reports have been reported relating to adverse renal consequences with prolonged pamidronate use.12,13 It is important to note that the appearance of renal dysfunction in these patients should lead the treating physician to hold the dose of pamidronate or zoledronic acid until there is resolution of the renal dysfunction. Based on the algorithm used in the comparative pamidronate versus zoledronic acid trials, if detected early, this renal dysfunction has been reversible in most cases. Retreatment of these patients with pamidronate or zoledronic acid has been tolerated without the return of kidney problems. Therefore, the development of renal dysfunction is cause for concern and warrants discontinuation of the drug until reversal of the renal abnormalities occurs. If the renal function does not return to normal, there are no data on which to base management. A prudent approach would be request consultation from a nephrologist and either indefinitely withhold bisphosphonate therapy or restart with close monitoring and a prolonged infusion time.

The Panel’s specific recommendation was that the presence of unexplained renal dysfunction should warrant discontinuation of pamidronate or zoledronic acid until these renal problems have resolved. Unexplained renal dysfunction is defined as an increase of ≥ 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels. These patients should be reassessed every 3 to
Evidence Summary

to monitor bisphosphonate use is not suggested for routine care. It is essential that physicians infuse pamidronate 90 mg at a rate no faster than 2 hours or zoledronic acid at a rate no faster than 15 minutes every 3 to 4 weeks and not attempt to shorten the infusion time, increase the dose, or reduce the dose interval.

The safety and frequency of nonrenal adverse events with zoledronic acid appear to be similar to pamidronate. The latter were well characterized in the pamidronate versus placebo trials\(^{14,15}\) and the recent pamidronate versus zoledronic acid studies.\(^{3,4}\) The incidence of most adverse effects in patients treated with pamidronate was similar to that observed in the placebo group. Transient myalgias, arthralgias, and flu-like symptoms with fever tend to occur more often in patients treated with pamidronate than placebo.\(^{15,16}\) These symptoms usually occur only after the first and/or second infusion of pamidronate and are not an indication to discontinue treatment of the drug. Ocular side effects from pamidronate are a relatively rare but well-recognized complication, first reported in 1994.\(^{17}\) An update review of case reports found 17 cases of unilateral scleritis and one case of bilateral scleritis, usually within 6 hours to 2 days after intravenous pamidronate. Six patients had positive rechallenge testing with the scleritis occurring again after a repeat drug exposure.\(^{18}\)

The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly.

The Panel deliberations focused on the lack of an operational definition of how regular is ‘regular’ blood chemistry assessment and the need to monitor serum creatinine prior to each dose of pamidronate or zoledronic acid. The FDA-approved labeling provides no guidance on time intervals for blood chemistry assessment, but is specific on pretreatment creatinine measurement. The Panel’s recommendation is consistent with the current FDA-approved guidelines in the pamidronate and zoledronic acid package inserts. Those guidelines were not part of the initial pamidronate package insert, but were changed in a recent revision. The Panel recognizes that it may be difficult or inconvenient for some clinics to obtain results of renal function tests before pamidronate or zoledronic acid administration. However, the Panel recommends that the FDA-approved monitoring guidelines be followed.

Biochemical Markers

2000 recommendation. The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.

2003 recommendation. No change.

Evidence Summary

Biochemical markers of bone resorption reflect the metabolic breakdown of type I collagen. Immunoassays have been developed to measure the N-terminal and C-terminal peptides of this collagen metabolism in urine and serum.\(^{19}\) Currently, only radiographic evidence of bone metastases is a reliable stratifier of future risk of bone complications. Biochemical markers could assist clinicians as either prognostic factors or predictive factors of treatment response to bisphosphonates.

Available preliminary studies show that bone marker levels, especially urinary N-telopeptide (NTX), correlate with the extent of bone involvement and bone progression.\(^{20}\) NTX was also found to be associated with future skeletal-related events, bone progression, and death in a recent report.\(^{21}\) In a retrospective study using data collected during the pamidronate-zoledronic acid comparative trial,\(^{9}\) baseline and serial bone markers were obtained from most patients. An elevated urinary NTX level at any time was associated in the subsequent 3 months with an increased risk of SRE, bone progression, or death. The relative risks reported for patients with an NTX greater than 100 nmol/mmol creatinine was 3.6 for a SRE, 3.2 for bone progression (not defined), and 6.7 for death, respectively.

However, the value of bone resorption markers to guide treatment decisions has not yet been shown, for example, to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bisphosphonate therapy, or to independently predict future fractures. Each is a worthy goal, but can only be addressed in the research setting.

Duration of Therapy

2000 recommendation. The panel suggests that once initiated, intravenous bisphosphonates be continued until evidence of substantial decline in a patient’s general performance status. The Panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

2003 recommendation. No change.

Role in Control of Pain Secondary to Bone Metastases

2000 recommendation. The Panel recommends that current standards of care for cancer pain, analgesics, and local radiation therapy should not be displaced by bisphosphonates. Intravenous pamidronate is recommended in women with pain as a result of osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2003 recommendation. The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radio pharmaceuticals, and local radiation therapy. Among other therapeutic options, intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic radiotherapy.
chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2000 recommendation. There is insufficient evidence to support a role for intravenous bisphosphonates as an adjunctive therapy to radiation therapy in women with pain as a result of metastatic bone disease when systemic chemotherapy and/or hormonal therapy is not being employed. The role of bisphosphonates vis-a-vis radiation therapy as the sole therapy in this setting has not been determined. In women already treated with local radiotherapy who have persistent or recurrent pain, bisphosphonates are an attractive but little studied salvage therapy.

2003 recommendation. No change.

Evidence Summary

A distinction should be made between the ability of bisphosphonates to relieve pain in patients with bone metastases from its ability to prevent pain from bone metastases.

A prospective case series by Groff et al. evaluated 200 patients with breast cancer or multiple myeloma who received 60 mg pamidronate in six infusions over 7 weeks, followed by one infusion every 3 weeks, for a total of 24 infusions concurrent with chemotherapy or radiation. Only 94 patients completed six infusions and only 25 patients completed all 24 infusions. The median equivalent daily dose of morphine ranged from 21 to 41 mg/d and either decreased or remained stable during the study. Given the lack of a control arm and concurrent therapy, the relative efficacy is difficult to interpret.

In the zoledronic acid versus pamidronate randomized, controlled clinical trial (discussed in detail in part I) the analgesic use stabilized or decreased in both groups, the median time to first SRE was approximately 12 months in all treatment groups, and the use of radiation therapy was decreased only among breast cancer patients treated with hormonal therapy.

For women with pain as a result of bone metastases, no studies have compared the efficacy of intravenous bisphosphonates to that of radiotherapy. Like the approach used in curative therapies of combining chemotherapy and radiation, studies are needed that evaluate the combination of radiation (external beam radiation and/or radiopharmaceuticals) with chemotherapy, hormonal therapy, and bisphosphonates. Part of the difficulty in determining the best multidisciplinary approach also relates to the various types of clinical problems that require palliative care. Issues that specifically need to be addressed are how therapies can be combined to create additive or synergistic effects to achieve the most rapid palliation of symptoms, fewest treatment-related toxicities, and least amount of time under treatment, especially in a patient with a limited prognosis. The optimal complementary role of bisphosphonates needs to be further defined.

The Role of Bisphosphonates With No Radiographic Evidence of Bone Metastases

Extraskeletal Metastases Without Evidence of Bone Metastases

2000 recommendation. Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extra-skeletal metastases is not recommended.

2003 recommendation. No change.

Bisphosphonates As Adjuvant Therapy

Since the 2000 guidelines were published, the three randomized controlled trials of adjuvant clodronate in early stage breast cancer have been updated. These three prospective randomized trials provide conflicting data on the potential role of adjuvant bisphosphonates among patients with no evidence of distant metastases after definitive local surgery. The findings from these studies were available in “first report” format at the time of publication of the 2000 guidelines, and each has since been updated. Table 2 provides a systematic tabular comparison of the trials.

The first trial conducted by Diel et al. randomly assigned 302 women with T1 to T4 and N0 to N2 primary breast cancer and immunocytochemical evidence of cancer (positive for tumor-associated glycoprotein-12) in a bone marrow aspirate to receive either clodronate 1,600 mg/d for 2 years or no bisphosphonate. The type of adjuvant systemic therapy was selected in accordance with specific guidelines. In the initial report, with a median follow-up of 36 months, the incidence of overall metastasis (13% v 29%), bone metastasis (8% v 17%), and visceral metastasis (8% v 19%) was more than cut in half (each P < .003). Particularly striking was the unanticipated finding that the clodronate group showed superiority in terms of metastasis-free survival and overall survival (96% v 85%; P = .001). The investigators provided an update of their initial report at the May 2000 ASCO meeting (New Orleans, LA). With an additional 2 years of follow-up, the extra-skeletal effect was no longer significant. However, the endpoints of reduction of bone metastases and improvement in disease-free survival (DFS) and overall survival (OS) remained statistically significant. At 5 years of follow-up, bone metastases were reduced in the clodronate group compared with a control group (14% v 24%; P = .044) and visceral metastases showed a trend toward reduction (17% v 26%; P = .091). Overall survival was higher in the clodronate arm (91% v 77%; P = .002). The effect of adjuvant clodronate appeared weakened with longer follow-up.

Powles et al. reported definitive results of their phase III trial presented in abstract form at the time of the 2000 guidelines. In this double-blind trial, 1,069 women were randomly assigned to receive either clodronate 1,600 mg/d or placebo starting 6 months after surgery, for a duration of 2...
<table>
<thead>
<tr>
<th>Specific Guideline</th>
<th>2000 Recommendation</th>
<th>2003 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonate use in women with imaging evidence of bone metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lytic disease on plain radiographs</td>
<td>Intravenous pamidronate at 90 mg delivered over 1 to 2 hours every 3 to 4 weeks is recommended in women with metastatic breast cancer who show lytic destruction of bone on plain radiograph(s), and who are receiving systemic therapy with hormonal therapy or chemotherapy</td>
<td>For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended. There is insufficient evidence relating to efficacy to support one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status and overall prognosis</td>
</tr>
<tr>
<td>Abnormal bone scan, normal radiographs but CT or MRI scan showing bone destruction</td>
<td>Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction and localized pain, but normal plain radiographs, is considered reasonable by panel consensus based on the findings in women with osteolytic changes on plain radiographs.</td>
<td>Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs.</td>
</tr>
<tr>
<td>Abnormal bone scan, normal radiographs and no evidence of bone destruction on CT or MRI</td>
<td>Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, tomograms, CT scans, or MRI, or with localized pain, is not suggested</td>
<td>Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.</td>
</tr>
<tr>
<td><strong>Safety and adverse effects</strong></td>
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<tr>
<td>Safety and adverse effects</td>
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<td>Safety and adverse effects</td>
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<tr>
<td>Safety and adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical markers</td>
<td>The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care</td>
<td>No change</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>The panel suggests that once initiated, intravenous bisphosphonates be continued until evidence of substantial decline in a patient’s general performance status. The panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.</td>
<td>No change</td>
</tr>
</tbody>
</table>
years. Although the type of systemic adjuvant therapy was not prescribed, the categories of no adjuvant therapy, chemotherapy, tamoxifen, or both chemotherapy and tamoxifen were balanced between the arms. The treatment arms were also balanced by stage and nodal status, and median follow-up was 5.5 years. Overall for the entire follow-up period, there was a nonsignificant decrease in the incidence of bone metastases (HR, 0.77; 95% CI, 0.56 to 1.08; P = .127) and there was no difference in the frequency of nonosseous metastases. During the 2 years of clodronate use, bone metastases were significantly lower in the group receiving clodronate compared with placebo (2.3% v 5.2%; P = .016); however, at 5 years follow-up, bone metastasis were no longer significantly different between the two treatment arms (12% v 15%; 95% CI, 0.06 to 1.08; P = .127). There was no difference in the frequency of nonosseous metastases. During the 2 years of clodronate use, bone metastases were significantly lower in the group receiving clodronate compared with placebo (2.3% v 5.2%; P = .016); however, at 5 years follow-up, bone metastasis were no longer significantly different between the two treatment arms (12% v 15%; 95% CI, 0.06 to 1.08; P = .127). No effect was observed on visceral sites of metastasis (17% v 20%; 95% CI, 0.06 to 1.08; P = .127). Overall survival, which was not a primary

### Table 1. Summary of Guidelines (continued)

<table>
<thead>
<tr>
<th>Specific Guideline</th>
<th>2000 Recommendation</th>
<th>2003 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role in control of pain secondary to bone metastases</td>
<td>The Panel recommends that current standards of care for cancer pain, analgesics and local radiation therapy should not be displaced by bisphosphonates. Intravenous pamidronate is recommended in women with pain as a result of osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.</td>
<td>The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radiopharmaceuticals, and local radiation therapy. Among other therapeutic options, intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.</td>
</tr>
<tr>
<td>There is insufficient evidence to support a role for intravenous bisphosphonates as an adjunctive therapy to radiation therapy in women with pain as a result of metastatic bone disease when systemic chemotherapy and/or hormonal therapy is not being employed. The role of bisphosphonates vis-à-vis radiation therapy as the sole therapy in this setting has not been determined. In women already treated with local radiotherapy who have persistent or recurrent pain, bisphosphonates are an attractive but little studied salvage therapy.</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>The role of bisphosphonates if no radiographic evidence of bone metastases Extraskeletal metastases without evidence of bone metastases</td>
<td>Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has not been studied using intravenous bisphosphonates and should be the focus of new clinical trials.</td>
<td>No change</td>
</tr>
<tr>
<td>Bisphosphonates as adjuvant therapy</td>
<td>Inconsistent, evolving data have been found in studies with bisphosphonate use in the adjuvant setting to prevent osseous metastases. Starting bisphosphonates in women at any stage of their nonosseous disease, outside of clinical trials, despite a high risk for future bone metastasis is currently not recommended.</td>
<td>No change</td>
</tr>
<tr>
<td>Bone health in women with a history of breast cancer Osteoporosis prevention</td>
<td>Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in premenopausal women with treatment-induced (usually secondary to chemotherapy) menopause.</td>
<td>Most women with newly diagnosed breast cancer are at risk of osteoporosis either because of their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of these women’s bone health. The panel recommended an algorithm for patient management to maintain bone health.</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FDA, Food and Drug Administration.
end point, was significantly improved in the clodronate arm (82% vs 76%; 95% CI, 0.59 to 1.00; P = .047). Further evaluation in a larger study is needed (see National Surgical Adjuvant Breast and Bowel Project [NSABP] B34 discussion).

Saarto et al24 reported results of a double-blind trial of 299 women with node-positive breast cancer who were randomly assigned to receive clodronate 1,600 mg/d or placebo for 3 years. All women received adjuvant therapy; premenopausal women received chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) and postmenopausal women received tamoxifen. The incidence of nonosseous metastases was significantly lower in the clodronate arm (10% vs 17%; P = .04). Both DFS and OS were significantly worse in the clodronate arm (DFS, 76% vs 83%; P = .09; OS, 70% vs 83%; P = .009). This apparent adverse effect of clodronate remained significant in the multivariate analyses after adjustment for other prognostic factors, including number of lymph nodes, tumor size, and hormone receptor status.

Therefore, there are three phase III prospective trials that address the role of adjuvant clodronate, two of which yielded favorable results and one that demonstrated an adverse impact. Given that the three trials are inconsistent, it remains uncertain whether bisphosphonates are beneficial and, if so, what is the optimal agent, route of therapy, dose, schedule, and duration of therapy. The intriguing but contradictory results of these three adjuvant bisphosphonate studies highlight the need for further investigation to determine whether bisphosphonates can influence the development of bone metastases and improve survival in early stage breast cancer.

The ongoing NSABP trial B34, in which 2,400 early stage breast cancer patients are randomly assigned to adjuvant clodronate or placebo, is a critical and definitive trial regarding clodronate. This trial, which should complete its accrual in 2003, will have its final analysis at 460 events (expected after 7 years) and is designed to detect a 23% reduction in the hazard rate for the primary end point of DFS. Additionally, the North American Intergroup will conduct an adjuvant bisphosphonate trial (S0307) comparing oral clodronate to newer, more potent bisphosphonates (risedronate, zoledronic acid). Finally, there is a growing role for the use of bisphosphonates in the prevention and treatment of osteoporosis (see next section on bone health), a major treatment issue in women undergoing systemic adjuvant therapy. More breast cancer patients will likely be receiving bisphosphonates for this indication in the future.

Table 2. Adjuvant Trials of Clodronate

<table>
<thead>
<tr>
<th>Design</th>
<th>Dial Study25</th>
<th>Pawles Study25</th>
<th>Saarto Study24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>302 patients</td>
<td>1069 patients</td>
<td>299 patients</td>
</tr>
<tr>
<td>Staging</td>
<td>50% node positive, 75% ER positive</td>
<td>37% node positive, 64% ER positive</td>
<td>100% node positive</td>
</tr>
</tbody>
</table>

Entry

| Pretreatment x-rays | Not reported | Not reported | 100% bone scintigraphy |
| Planning |
| End point assessment schedule | Every 3-4 m 1st 2 years | Every 3 m 1st year; every 6 m 2-5 years | Every 4 to 6 m |
| Preplanned primary endpoint | Development of bone metastases | Development of bone metastases | Development of bone metastases |
| Prestudy power calculation | 10% absolute difference in bone metastases | 25% reduction in bone metastases at 60 m; 50% reduction in bone metastases on treatment | 10-15% absolute reduction in bone metastases |
| Radiographs read blind and independently | Yes | Not reported | Not reported |
| Intent to treat analysis | Yes | Yes, secondary | |

Follow-up

| Imaging completed during follow-up | Annual chest x-ray, bone scan, liver ultrasound; x-rays if clinically indicated | At 24 m, 60 m and as indicated | Scintigraphy 1, 2, 3 and 5 years, x-rays if clinically indicated |

Bony metastases

| Primary endpoint | 8% c vs 17% p at 36 m; P = .003 | 3.8% c vs 6.7% p at 24 m (while on treatment); P = .016 | Not reported |
| At 5 years | 14% c vs 24% p; P = .04 | 11.1% c vs 10.2% p; P = .127 | 21% c vs 17% p |

Survival

| Primary end point | 4% c vs 15% p at 36 m; P = .001 | 92.7% c vs 92.4% p at 24 mo; P = .21 | 70% c vs 83% p; P = .009 |
| At 5 years | 91% v 77% p; P = .002 | 82.9% v 79.3% p; P = .047 | |

Summary

| Relative risk | 0.70 (calculated) at 36 m | 0.44 (0.22-0.86); P = .016 at 2 years | NA, increased risk |
| | 0.41 (calculated) at 5 years | 0.77 (0.56-1.08); P = .127 at 5 years | NA, increased risk |

Abbreviations: c, clodronate; p, placebo; ER, estrogen receptor; m, months; NA, not applicable.
future, which will potentially confound the interpretation of the adjuvant trial literature.

At present, adjuvant clodronate cannot be recommended as a standard of care for any women about to undergo systemic adjuvant therapy, yet these trials provide provocative data worthy of establishing hypotheses for prospective studies.

**BONE HEALTH IN WOMEN WITH A HISTORY OF BREAST CANCER**

**Osteoporosis Prevention**

2000 recommendation. Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in premenopausal women with treatment-induced (usually secondary to chemotherapy) menopause.

2003 recommendation. Most women with newly diagnosed breast cancer are at risk of osteoporosis due to either their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of these women’s bone health. The Panel recommended an algorithm for patient management to maintain bone health.

**Evidence Summary**

Osteoporosis is an increasingly common problem in women with diagnosed breast cancer. Evidence now supports strategies for osteoporosis screening, prevention and therapy in otherwise healthy women. Current information regarding osteoporosis prevention and therapy is outlined in the next section. This outline summarizes the additional risks of osteoporosis development associated with a breast cancer diagnosis. The available information on osteoporosis prevention and therapy in breast cancer patients is outlined and, largely by inference, a strategy for osteoporosis screening, prevention, and therapy for breast cancer patients without evidence of bone metastases is described.

Women with a breast cancer diagnosis are at increased risk for osteoporosis and fracture. In one study, the presence of even localized breast cancers in women without evidence of bone metastases is described. Evidence now supports strategies that should trigger screening were not specified, but low body weight (<70 kg) and prior fracture history are strong risk predictors. Based on limited evidence, USPSTF made no recommendation regarding routine screening in any other women.

**General principles of osteoporosis prevention and therapy**. Preventing osteoporotic fractures can be achieved by maximizing peak skeletal mass, preventing or slowing rates of bone loss, and preventing falls. Fundamental measures for bone health include adequate calcium intake (1,200 mg/d), and vitamin D intake (400 to 800 U), exercise, and avoidance of smoking. Women who should receive osteoporosis therapy include those with prior fragility fractures, as well as women with a BMD t score ≤−2.5. Treatment of women without fractures but who have borderline low BMD (t score < −1.0) and other risk factors is controversial and should be decided on an individual basis.

The Osteoporosis Research Advisory Group (ORAG) has provided a comprehensive review of the randomized trials of osteoporosis therapies. Vitamin D (hydroxylated), calcitonin, raloxifene, the bisphosphonates, etidronate, risedronate, and alendronate all reduced vertebral fractures with the strongest data supporting alendronate and risedronate. Only alendronate and risedronate significantly reduced nonvertebral fractures. The particular issues relevant to women with breast cancer are summarized in Table 3. In postmenopausal women, tamoxifen had modest influence on BMD and fracture risk, but is not considered a stand-alone osteoporosis therapy. Raloxifene is approved for osteoporosis prevention and therapy exclusively in postmenopausal women. There are reservations regarding use of raloxifene following 5 years of tamoxifen adjuvant therapy because raloxifene has limited activity against advanced breast cancer when used after tamoxifen, and 10 years of tamoxifen has been associated with more recurrences than stopping tamoxifen after 5 years. Other agents not currently approved by the FDA for osteoporosis prevention may also
influence fracture risk and include tibolone, strontium, and bisphosphonates clodronate, ibandronate, pamidronate, tiludronate, and zoledronic acid. This latter bisphosphonate, in one randomized trial, reversed osteoporosis BMD with a 4 mg intravenous annual infusion.

After the ORAG report was released, teriparitide, a synthetic parathyroid hormone, was approved for osteoporosis therapy. However, because this drug was associated with osteosarcoma development in animal studies, it is not recommended for use in patients with diagnosed breast cancer. In addition, the recent report indicating more overall risk versus benefit for estrogen plus progestin use, including increased breast cancer risk, makes use of menopausal hormones for osteoporosis prevention in breast cancer patients especially problematic.

Postmenopausal adjuvant therapy. Trends in adjuvant hormonal therapy indicate that osteoporosis will become a greater clinical problem in the future. The relative percentage of breast cancer that is estrogen receptor–positive increases with age and peaks at approximately 75% in women over 70 years of age.

For such women with advanced breast cancer, use of progestins (largely felt to be neutral with respect to bone density) is being replaced by aromatase inhibitors, which are associated with bone loss and increased fracture risk. In the adjuvant setting, the aromatase inhibitor anastrozole is approved by the FDA for postmenopausal women with early stage receptor-positive breast cancer. When used in that setting, it replaces tamoxifen, a drug associated with increased bone density and reduced fracture risk. In the large anastrozole, tamoxifen, alone or in combination (ATAC) trial in postmenopausal women with early stage breast cancer, anastrozole significantly increased fracture risk compared with tamoxifen (incidence of 7.1% seen on anastrozole vs. 4.1% on tamoxifen after a mean of 37 months follow-up; OR, 1.34; 95% CI, 1.22 to 1.57). In a subset of 300 ATAC patients who had baseline and 1-year later biochemical markers of bone turnover and bone mineral density (BMD) assessments, anastrozole patients had increased bone resorption markers and decrease in spine and hip BMD, and in the tamoxifen patients, the converse occurred. Indirect comparison suggest about a third of the excess fracture risk seen with anastrozole in the ATAC trial is related to absence of a tamoxifen effect.

Although raloxifene is approved for osteoporosis prevention and therapy, its use following 5 years of tamoxifen adjuvant therapy is not recommended. This is based on the fact that raloxifene and tamoxifen are similar agents and 10 years of treatment is associated with increased fracture risk.

Table 3. Therapies Available for Osteoporosis Prevention and Therapy: Approved by US FDA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosage</th>
<th>Common Side Effects</th>
<th>Issues for Use in Breast Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approved bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>5 mg PO daily</td>
<td>Upper GI irritation, myalgias and arthralgias</td>
<td>None</td>
</tr>
<tr>
<td>Prevention and treatment</td>
<td>35 PO weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 PO weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>5 mg PO daily</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Prevention and treatment</td>
<td>35 PO weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective estrogen receptor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>modulator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60 mg PO daily</td>
<td>Common: Hot flashes, leg cramps; rare: deep vein thromboses</td>
<td>Cross resistance with tamoxifen; not recommended after tamoxifen</td>
</tr>
<tr>
<td>Prevention and treatment</td>
<td>20 U SQ daily</td>
<td>Common: dizziness, leg cramps; rare: hypercalcemia</td>
<td>Not recommended; Should not be used in patients at increased risk of bone metastases or hypercalcemia (due to osteosarcoma development in animal models)</td>
</tr>
<tr>
<td>Parathyroid Hormone (synthetic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparitide</td>
<td>20 U SQ daily</td>
<td>Common: dizziness, leg cramps; rare: hypercalcemia</td>
<td>Not recommended; Should not be used in patients at increased risk of bone metastases or hypercalcemia (due to osteosarcoma development in animal models)</td>
</tr>
<tr>
<td>Estrogen plus progestin</td>
<td>Varies</td>
<td>Common: breast tenderness, vaginal bleeding; life threatening: CHD, stroke, PE, breast cancer</td>
<td>Not recommended in patients with a breast cancer diagnosis when used for osteoporosis prevention</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five combination agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nine agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>1200 mg/d</td>
<td>Constipation, bloating, gas</td>
<td>None</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400-600 mg</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Calcitonin nasal spray</td>
<td>200 U one nostril/day</td>
<td>Rhinitis</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; PO, orally; SQ, subcutaneous; GI, gastrointestinal; CHD, coronary heart disease; PE, pulmonary embolism.
tamoxifen use has been associated with more recurrences and deaths than 5 years of tamoxifen.\(^\text{42}\) In addition, laboratory studies show that raloxifene may stimulate tamoxifen-dependent cells.\(^\text{54}\) Concurrent use of raloxifene and aromatase inhibitors is not recommended based on the adverse effect of combining tamoxifen with anastrozole in the ATAC trial.\(^\text{51}\)

Premenopausal therapy. Regardless of receptor status, many premenopausal women with early stage breast cancer are at risk of chemotherapy associated premature menopause,\(^\text{55-57}\) which results in rapid bone loss comparable to that seen with surgical oophorectomy (7.7% loss in lumbar spine BMD in one report).\(^\text{57}\) Use of adjuvant taxanes can further increase the frequency of premature menopause.\(^\text{58}\) Premenopausal women treated with ovarian suppression without concurrent tamoxifen are at similar levels of bone loss risk. Concurrent tamoxifen use in this setting may not be protective since some studies have suggested that tamoxifen itself is associated with loss of bone density in premenopausal women.\(^\text{59}\)

**Bisphosphonates in combination with adjuvant therapy in breast cancer patients without bone metastases.** The effect on bone mineral density of bisphosphonates with hormonal or cytotoxic chemotherapy is being evaluated in comparative trials. In a small trial of 120 postmenopausal breast cancer patients without skeletal metastases, women were randomly assigned to one of two selective estrogen receptor modulators (SERMs), either tamoxifen or toremifene and, in a factorial design, had a second randomization to oral clodronate 1,600 mg daily or control (no bisphosphonate). At 2 years, clodronate together with a SERM markedly increased lumbar spine BMD by 2.9% \((P = .001)\) while patients receiving the SERM alone did not significantly increase BMD.\(^\text{59}\)

For breast cancer patients given adjuvant CMF chemotherapy, significantly less BMD loss occurred in women randomly assigned to oral clodronate compared with placebo.\(^\text{60}\) Currently, there is only one report on the efficacy of oral bisphosphonates FDA approved for osteoporosis therapy in the United States in a breast cancer population at risk for bone loss. In a 52 patient randomized trial, the bisphosphonate risedronate taken as 30 mg per day for 2 weeks followed by 10 weeks of no drug, was shown to prevent bone loss in young women with breast cancer and premature chemotherapy induced menopause.\(^\text{61}\)

In a promising preliminary report, premenopausal breast cancer patients receiving goserelin plus anastrozole or goserelin plus tamoxifen were randomly assigned to the bisphosphonate zoledronic acid (4 mg IV q 6 months) or placebo. After 6 months, those receiving zoledronic acid had significantly higher lumbar spine BMD \((P < .0001)\).\(^\text{53}\) Completion of this trial is needed before the Panel can make a specific recommendation. Currently, there are no reports of the use of calcium and vitamin D in breast cancer patients free of bone metastases.

**Bone health summary.** In otherwise healthy women, a strong body of evidence supports a strategy of early detection and therapy of osteoporosis. Similar recommendations can be applied to breast cancer patient management, as shown in Figure 1. Breast cancer patients identified by their history to be at high risk for osteoporosis should be evaluated by BMD. As in women without breast cancer, subsequent interventions are guided by BMD results. Current evidence is insufficient to support intravenous pharmacologic interventions to maintain normal BMD in any subgroup of breast cancer patients without bone metastases.

Breast cancer patients found to have osteoporosis based on BMD results \((t \text{ score } \leq -2.5 \text{ or lower})\) should have pharmacologic therapy initiated with an agent demonstrated to have efficacy. There is currently insufficient evidence to recommend a particular agent in this category. Breast cancer patients found to have osteopenia based on BMD results \((t \text{ score between } -1 \text{ and } -2.5)\) should have their therapy individualized, but current evidence cannot support routine intervention with bisphosphonates for this group.

**COMMENTARY: PUBLIC POLICY AND COST-UTILITY IMPLICATIONS**

Prior cost-effectiveness analyses have suggested that the cost-savings from bisphosphonates and/or radiation in reducing bone complications were insufficient to offset the costs associated with the bisphosphonates and their delivery.\(^\text{62-64}\) Since 2000, there have been new cost-effectiveness assessments of bisphosphonates in breast cancer.

There is new retrospective data indicating that a reduction in medical services is probably the case with intravenous bisphosphonates, but that the initial characteristics of patients receiving pamidronate substantially differ. The chart review study involving 12 community U.S. oncology sites compared women who initiated pamidronate within 3 months (early) of bone metastasis diagnosis or after 3 months (late) of diagnosis with patients who never (none) received pamidronate between July 1996 and April 1999.\(^\text{64}\) 295 patients were identified. Patients receiving early pamidronate were more likely to have multiple bone lesions, a serious initial event or hypercalcemia. Pamidronate-treated patients needed less radiotherapy and the duration of hospitalizations were about 50% shorter than nonpamidronate patients.

With the recent approval of zoledronic acid in the United States, the decision facing most oncologists will be whether to switch from pamidronate to zoledronic acid. In 2001, generic pamidronate became available. In 2003, there are at least four suppliers of generic pamidronate. In an ideal world, competition would drive down the price of pamidronate; however, current US average wholesale prices of pamidronate have changed minimally since the introduction of generic versions.

Pamidronate’s longer infusion time compared with zoledronic acid (2 hours v 15 minutes) is associated with an opportunity for lower cost to the patient (their time), the cancer location (use of infusion chair), and extra staff time (reflected in common procedural terminology codes). A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid versus pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour, 6 minutes, compared to 2 hours, 52 minutes for pamidronate patients.\(^\text{55}\) From the infusion center perspective, the opportunity benefit for zoledronic acid was an average increase in 1.8 chairs per day available for other patients.

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The choice of bisphosphonates is broader in number and delivery method (oral vs intravenous) outside the U.S. Where oral clodronate is available, the price difference between available bisphosphonates is commonly minimal, and the absolute cost for any bisphosphonate is much lower per standard treatment interval. Pamidronate and zoledronic acid have acquisition prices in most of Europe that are 40% to 70% less than the U.S. Therefore, each country must make its own relative cost-benefit assessment.

ONGOING AND FUTURE RESEARCH

Ongoing and future clinical trials with bisphosphonates in breast cancer include metastatic trials investigating optimal use of approved agents, as well as promising new drugs, adjuvant trials evaluating a potential prevention role for bisphosphonates, and studies looking at minimizing cancer treatment-related loss of bone mineral density.

Metastatic breast cancer. In metastatic breast cancer, the major unanswered questions listed in the 2000 guidelines regarding bisphosphonates remain unanswered and uninvestigated. These include the optimal drug, dosing, route of delivery, duration of therapy, timing of initiation of drug, and toxicity monitoring. New amino-bisphosphonates are in varying phases of clinical development.

Ibandronate, a third generation bisphosphonate, is approved in intravenous form for treatment of hypercalcemia of malignancy in over 50 countries outside the United States. Phase III studies of both oral and intravenous ibandronate compared with placebo have recently been completed.\textsuperscript{66,67} In 2002 and 2003, the Panel made written requests to Hoffman LaRoche (Nutley, NJ) for data. No responses were received. Data on the oral ibandronate studies were presented at the ASCO meeting in 2003.\textsuperscript{67} (This summary is based on published reports only). A pooled analysis of two randomized, double blind, placebo-controlled phase III trials of oral ibandronate (50 mg and 20 mg) versus placebo was performed among breast cancer patients with bone metastases. Significant improvements in the primary end point and the skeletal morbidity rate were observed for both oral doses of ibandronate when compared with placebo. A supplemental application was filed in late 2002 with the European Agency for the Evaluation of Medicinal Products for the treatment of bone metastases in breast cancer patients with both oral and intravenous versions of ibandronate. The Southwest Oncology Group (SWOG) trial S0308 will evaluate oral ibandronate (50 mg daily) in breast cancer patients with bone metastases as compared to zoledronic acid (4 mg intravenous monthly), with time to first skeletal-related event as the primary study end point.
Adjuvant breast cancer. The intriguing but contradictory results of the three adjuvant bisphosphonate studies reported to date highlight the need for further investigation. The NSABP protocol B34 is evaluating oral clodronate for 3 years versus placebo in addition to standard treatment in 2,400 patients with stage I or II breast cancer. At the closure of NSABP B34, the North American Intergroup will initiate a 6,000 patient, three-arm adjuvant bisphosphonate trial (S0307, lead by SWOG) comparing 3 years of oral clodronate to two newer, more potent bisphosphonate agents, oral risedronate and intravenous zoledronic acid. A multinational Adjuvant Zoledronic Acid Reduce Recurrence study, also soon to begin accrual, is a prospective, randomized, open-label trial to determine if adjuvant treatment with zoledronic acid plus standard systemic therapy is superior to systemic therapy alone in improving DFS.

If benefit for bisphosphonates is proven in the adjuvant breast cancer setting, we will need to carefully address the optimal agent, dose, schedule, and duration of therapy. Whether doses used in metastatic disease are required for prevention, or whether lower doses would suffice, is unknown. It is unclear whether adjuvant bisphosphonates should be given continuously and orally, or whether intermittent intravenous therapy would be preferable. The optimal duration of therapy is also unknown, with current studies suggesting that 2 years is an insufficient treatment length. Long-term follow-up will be needed to determine if bisphosphonates are actually able to prevent or merely delay bone lesions.

Incorporated into the upcoming adjuvant bisphosphonate trials are correlative studies investigating the use of markers to select high-risk women. Ultimately, we would hope to determine which breast cancer patients might benefit most from adjuvant bisphosphonates by evaluating tumor characteristics, urine or serum markers, or bone marrow findings that predict who is at highest risk for bone recurrence.

Cancer treatment-related bone loss. Irrespective of the development of bone metastases, it is possible that all early stage breast cancer patients could benefit from bisphosphonates in the form of preservation of bone density. Adjuvant aromatase inhibition in postmenopausal patients and ovarian suppression in premenopausal patients are the subject of ongoing studies.

The final report of the Austrian Breast Cancer Study Group randomized trial of zoledronic acid in premenopausal women treated with hormonal therapy (discussed in the osteoporosis section) is eagerly anticipated.

The international pharmaceutical company-sponsored Zometa/Femera Adjuvant Synergy Trial study is an open-label, randomized, multicenter study evaluating the use of zoledronic acid in the prevention of cancer treatment-related bone loss in postmenopausal breast cancer patients receiving letrozole as adjuvant therapy. The International Breast Cancer Intervention Study II comparing anastrozole to placebo in women at high risk of developing breast cancer, and tamoxifen to anastrozole in ductal carcinoma in situ, has subprotocols including a bisphosphonate examining the effects of risedronate on prevention of bone loss associated with anastrozole. CALGB protocol 79809 is a phase II trial of intravenous zoledronic acid for the prevention of bone loss among localized breast cancer patients with chemotherapy-induced ovarian failure.

Other osteoclast-targeted therapies. Additionally, non-bisphosphonate compounds that interfere with bone metabolism are under investigation in breast cancer patients with bone metastases. Agents of interest include anti-RANK ligand pathway-targeted therapy, and anti-parathyroid hormone-related peptide antibodies.

ACKNOWLEDGMENT

The Expert Panel wishes to express its gratitude to Drs Harold Burstein and Gabriel N. Hortobagyi for their thoughtful reviews of earlier versions of these guidelines.

APPENDIX

Bisphosphonates in Breast Cancer Expert Panel

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Bruce E. Hillner, MD, Chair</td>
<td>Virginia Commonwealth University, Richmond, VA; HSR and Med Onc</td>
</tr>
<tr>
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<td>Mayo Clinic, Rochester, MN; Med Onc</td>
</tr>
<tr>
<td>Kathy S. Albain, MD</td>
<td>Loyola University Medical Center, Maywood, IL; Med Onc</td>
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<tr>
<td>Susan Brown, MS, RN</td>
<td>The Susan G. Komen Breast Cancer Foundation, Dallas, TX; Pat/Adv Rep</td>
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<tr>
<td>Brent A. Blumenstein, PhD</td>
<td>Tri Arc Consulting, Seattle, WA; BioStat</td>
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<tr>
<td>Jane A. Cauley, DrPH</td>
<td>University of Pittsburgh, Pittsburgh, PA; Epistat</td>
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<tr>
<td>Rowan T. Chlebowski, MD, PhD</td>
<td>Harbor UCLA Medical Center, Torrance, CA; Med Onc</td>
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<tr>
<td>Julie Gralow, MD</td>
<td>University of Washington, Seattle, WA; Med Onc</td>
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<tr>
<td>Nora A. Janjan, MD</td>
<td>M.D. Anderson Cancer Center, Houston, TX; Rad Onc</td>
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<td>Allan Lipton, MD</td>
<td>Milton S. Hershey Medical Center, Hershey, PA; Med Onc</td>
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<tr>
<td>Gary C. Yee, Pharm D</td>
<td>University of Nebraska Medical Center, Omaha, NE; Pharm</td>
</tr>
</tbody>
</table>

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES


47. Writing Group for the Women’s Health Initiative: Risks and benefits of estrogen plus progester in healthy postmenopausal women: principal results from the women’s health initiative randomized controlled trial. JAMA 288:321-333, 2002


ERRATA

The March 15, 2003 article by Giles et al entitled “Randomized Phase I/II Study of Troxacitabine Combined With Cytarabine, Idarubicin, or Topotecan in Patients With Refractory Myeloid Leukemias” (J Clin Oncol 21:1050-1056, 2003) contained two errors. In the Abstract and Table 1, the dose of cytarabine is given in mg (milligrams), while it should have been in g (grams).

DOI: 10.1200/JCO.2004.02.910

The November 1, 2003 ASCO Special Article by Hillner et al entitled, “American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer” (J Clin Oncol 21:4042-4057, 2003) contained an error in Table 3. The dosage for vitamin D was given as 400-600 mg. The authors would like to state that 1 unit of vitamin D equals 0.025 μg of cholecalciferol (vitamin D3). Experts recommend a daily intake between 400 and 800 U of vitamin D. Most multivitamins contain 400 U. Commercial forms of vitamin D3 are supplied in either 400- or 1000-U tablets.

DOI: 10.1200/JCO.2004.01.990
American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

ABSTRACT

Purpose
To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.

Methods
An expert panel and a writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature from 1987 to 2005 was performed, and included a search of online databases and consultation with content experts.

Results
The literature review found many cohort studies, case series, and case reports, but relatively few randomized or definitive trials examining the success and impact of fertility preservation methods in people with cancer. Fertility preservation methods are used infrequently in people with cancer.

Recommendations
As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.

Conclusion
Fertility preservation is often possible in people undergoing treatment for cancer. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning.

The purpose of this guideline is to review the literature pertaining to fertility preservation options for men, women, and children undergoing cancer treatment, and to give guidance to oncologists about these issues. The focus is restricted to interventions aimed at fertility preservation; the guidelines do not address methods of fertility restoration after completion of cancer treatment nor the risks of assisted reproductive techniques, except those unique to cancer patients. The risks of pregnancy to parents and offspring after cancer treatment are reviewed only insofar as they might affect a person’s desire to pursue fertility preservation methods before or during active cancer treatment.

Estimating the Risk of Infertility After Treatment for Cancer
Infertility is functionally defined as the inability to conceive after 1 year of intercourse without

INTRODUCTION

The diagnosis and treatment of cancer often poses a threat to fertility. Methods of fertility preservation are evolving quickly, yet little has been published in the medical oncology literature regarding this topic. Studies suggest that the ability to have biological children is of great importance to many people. Any oncologist seeing reproductive-aged patients for consideration of cancer therapy should be addressing potential treatment-related infertility with them or, in the case of children, with their parents. Yet, studies suggest that many oncologists either do not discuss the possibility of treatment-related infertility or do so suboptimally. Teaching in many fellowship programs covers sperm banking and techniques such as oophorectomy, while little information is provided concerning other methods of fertility preservation.
contraception. Rates of permanent infertility and compromised fertility after cancer treatment vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or size/location of the radiation field, dose, dose-intensity, method of administration (oral versus intravenous), disease, age, sex, and pre-treatment fertility of the patient. Male infertility can result from the disease itself (best documented in patients with testicular cancer and Hodgkin’s lymphoma), anatomic problems (eg, retrograde ejaculation or anejaculation), primary or secondary hormonal insufficiency, or more frequently, from damage or depletion of the germinal stem cells. The measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity. In females, fertility can be compromised by any treatment that decreases the number of primordial follicles, affects hormonal balance, or interferes with the functioning of the ovaries, fallopian tubes, uterus, or cervix. Anatomic or vascular changes to the uterus, cervix, or vagina from surgery or radiation may also prevent natural conception and successful pregnancy, requiring assisted reproductive technology or use of a gestational carrier.

Male and female fertility may be transiently or permanently affected by cancer treatment or only become manifest later in women through premature ovarian failure. The panel wishes to emphasize that female fertility may be compromised despite maintenance or resumption of cyclic menses. Regular menstruation does not guarantee normal fertility as any decrease in ovulatory reserve may result in a lower chance of subsequent conception and higher risk of early menopause. Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened by premature menopause.

An estimated 1,372,910 people were diagnosed with cancer in 2005, of whom 4% (approximately 55,000) are under the age of 35. The most common cancers diagnosed in people under the age of 40 years are breast cancer, melanoma, cervical cancer, non-Hodgkin’s lymphoma, and leukemia. The Panel recognizes that a table of all common cancer treatments with their associated risks of infertility is desirable. However, available data are poor and heterogeneous, so summarization was felt to be beyond the scope of this guideline. However, Tables 1A and 2, and several additional references illustrate the range of risks associated with several cancer therapies. The Panel noted that most of the available literature quantifying infertility risks reports rates of azoospermia and amenorrhea, though these are surrogate measures of infertility. In men and women, the greatest risks associated with chemotherapy involve the alkylating agents (particularly cyclophosphamide, 

<table>
<thead>
<tr>
<th>Table 1. Effects of Different Antitumor Agents on Sperm Production in Men</th>
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<tbody>
<tr>
<td><strong>Agents (Cumulative Dose for Effect)</strong></td>
</tr>
<tr>
<td>Radiation (2.5 Gy to testis)</td>
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<tr>
<td>Chlorambucil (1.4 g/m²)</td>
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<td>Cyclophosphamide (19 g/m²)</td>
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<td>Procarbazine (4 g/m²)</td>
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<tr>
<td>Melphalan (140 mg/m²)</td>
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<tr>
<td>Cisplatin (500 mg/m²)</td>
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<tr>
<td>BCNU (1 g/m²)</td>
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<tr>
<td>CCNU (500 mg/m²)</td>
</tr>
<tr>
<td>Busulfan (600 mg/kg)</td>
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<tr>
<td>Ifosfamide (42 g/m²)</td>
</tr>
<tr>
<td>BCNU (300 mg/m²)</td>
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<tr>
<td>Nitrogen mustard</td>
</tr>
<tr>
<td>Actinomycin D</td>
</tr>
<tr>
<td>Carboplatin (2 g/m²)</td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin) (770 mg/m²)</td>
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<tr>
<td>Thiotepa (400 mg/m²)</td>
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<tr>
<td>Cytosine arabinoside (1 g/m²)</td>
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<tr>
<td>Vinblastine (IS g/m²)</td>
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<tr>
<td>Vincristine (8 g/m²)</td>
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<tr>
<td>Amsacrine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, 5-fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine</td>
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<tr>
<td>Prednisone</td>
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<td>Interferon-α</td>
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<td>Examples of new agents:</td>
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<tr>
<td>Oxaliplatin</td>
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<tr>
<td>Irinotecan</td>
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<tr>
<td>Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)</td>
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<td>Tyrosine kinase inhibitors (erlotinib, imatinib)</td>
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<tr>
<td>Taxanes</td>
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NOTE. Reprinted and modified Table 54.6-3 with permission from DeVita, VT, Jr, Hellman S, and Rosenberg, SA. Cancer: Principles & Practice of Oncology (ed 7). Philadelphia, Pa, Lippincott Williams & Wilkins, 2005. Abbreviations: BCNU, carmustine; CCNU, lomustine.
Table 2. Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Cancer Treatment</th>
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| High risk (>80%)     | Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan.  
                       | External beam radiation to a field that includes the ovaries.  
                       | CMF, CEF, CAF × 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, etoposide) |
| Intermediate risk    | CMF, CEF, CAF × 6 cycles in women age 30-39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, etoposide)  
                       | AC × 4 in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide) |
| Lower risk (<20%)    | ABVD (doxorubicin/bleomycin/vinblastin/dacarbazine)  
                       | CHOP × 4-6 cycles (cyclophosphamide/doxorubicin/vincristine/prednisone)  
                       | CVP (cyclophosphamide/vincristine/prednisone)  
                       | AML therapy (anthracycline/cytarabine)  
                       | ALL therapy (multi-agent)  
                       | CMF, CEF, CAF × 6 cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, etoposide)  
                       | AC × 4 in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide) |
| Very low or no risk  | Vincristine  
                       | Methotrexate  
                       | 5-fluorouracil |
| Unknown risk (examples) | Taxanes  
                       | Oxaliplatin  
                       | Irinotecan  
                       | Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)  
                       | Tyrosine kinase inhibitors (erlotinib, imatinib) |

*These are general guidelines based on best available literature. Additional factors, particularly pre-treatment ovarian reserve, specific treatment regimen, and age determine individual risk for immediate infertility, or for premature ovarian failure after resumption of menses. Please see text for details.

ifosfamide, nitrosoureas, chlorambucil, melphalan, busulfan, and procarbazine). Total-body irradiation as used in myeloablative stem-cell transplantation is highly associated with infertility, while lesser doses or limited radiation fields have less gonadal toxicity.\textsuperscript{13,14} Several agents are associated with a low or no risk of infertility: methotrexate, fluorouracil, vincristine, bleomycin, and dacinomycin. There are little human data available for the newer agents such as taxanes. Given the paucity of data regarding rates of male and female infertility following most current cancer treatments and the large number of patient factors that influence fertility, oncologists may have difficulty providing precise guidance to patients about their risks for infertility.

Questions The committee addressed the following clinical questions:

1. Are cancer patients interested in interventions to preserve fertility?
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?
4. What is the role of the oncologist in advising patients about fertility preservation options?

Practice Guidelines Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide the following:

1. Improvement in outcomes
2. Improvement in medical practice
3. Means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where further research is needed

In formulating recommendations for fertility preservation options, ASCO considered these tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. However, it is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. (Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances. In addition, these guidelines describe the use of procedures and therapies in clinical practice; they cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.)

Panel Composition

The ASCO Health Services Committee (HSC) convened an Expert Panel consisting of experts in clinical medicine and research relevant to fertility preservation in cancer patients, including adult and pediatric oncology, obstetrics-gynecology, andrology, reproductive endocrinology and infertility, health services research,
psychosocial oncology, and bioethics. A patient representative was also part of the Panel. Panel members are listed in the Appendix.

**Literature Review and Analysis**

The following electronic databases were searched from 1987 through March 2005: MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. The National Cancer Institute’s (NCI) PDQ database of clinical trials, and the National Library of Medicine’s (NLM) ClinicalTrials.gov database were also searched for ongoing trials. Results were supplemented with hand searching of selected reviews and personal files. The following MeSH terms and text words were used in a core search: “fertility,” “infertility,” and “neoplasms.” In separate searches, results were cross-referenced with “pregnancy,” “pregnancy outcomes,” “reproductive techniques,” “premature ovarian failure,” and “premature menopause.” Supplemental searches were done for each intervention using terms specific for that intervention (eg, “sperm banks,” “semen preservation”). Due to the very limited number of randomized controlled trials in this field of research, study design was not limited to randomized controlled trials, but was expanded to include cohort designs, case series, and where no other data were available, case reports and selected abstracts. Letters, commentaries, and editorials were excluded.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the study discussed a fertility intervention and reported primary data; and (2) the study population consisted of cancer patients scheduled for or undergoing cancer treatments that threaten fertility (other populations could be considered where data were lacking in cancer patients). Articles were excluded from further consideration if they did not report specifically on a fertility intervention and did not report primary data. However, due to the limited nature of the data in many areas, the Panel made an a priori decision to also retain high-quality reviews or background papers, and these articles were described as such in the coding process.

An initial article abstract screen was performed by ASCO staff. The ASCO Panel reviewed all remaining potentially relevant abstracts identified in the original literature searches to select studies pertinent to its deliberations. Two Panel members independently reviewed each abstract for its relevance to the clinical questions, and disagreements were resolved by third-party review. Full text articles were then reviewed for all selected abstracts. The Panel designed a coding sheet to complete the review of identified potentially relevant studies, and the Co-Chairs assigned each Panel member a subset of articles to review. Data were extracted on the source of the threat to fertility, the intervention being considered, the outcomes assessed, the number of patients and types of cancer, and study design. Primary outcomes of interest included pregnancies and live births, but the following were also considered: fertility maintenance; resumption/maintenance of menses; number of oocytes recovered; number of embryos recovered; fertilization rates; and in vitro fertilization (IVF) outcome. Also considered were the risks associated with the fertility intervention, quality of life, patient and/or family satisfaction, patient education or increased awareness, and economic evaluation (eg, cost-effectiveness, cost utility).

**Consensus Development Based on Evidence**

The entire Panel participated in monthly teleconferences. Preliminary teleconferences refined the questions addressed by the guideline; subsequent teleconferences addressed the process of the systematic review and the allocation of writing assignments for respective sections. All members of the Panel participated in the preparation of the guideline. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the Health Services Committee (HSC) and by the ASCO Board of Directors before dissemination.

**Guideline and Conflict of Interest**

All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO’s disclosure form and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual’s role should be limited as a result of a conflict. No limiting conflicts were identified.

**Revision Dates**

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the HSC and the ASCO Board for review and approval.

**RESULTS**

**Literature Search**

Preliminary searches identified 1,675 potential articles. The initial abstract screen performed by ASCO staff eliminated 807 abstracts that failed to meet any of the inclusion criteria. The ASCO Panel conducted dual independent review of all remaining 868 potentially relevant abstracts identified in the original systematic review. The Panel eliminated 463 abstracts at this stage of the review; the remaining 405 articles were reviewed in full for the interventions and outcomes described above. One hundred twenty-nine articles that did not report primary data on a fertility preserving intervention were excluded from further consideration. Two hundred thirty-three articles met the inclusion criteria, and an additional 43 articles met the a priori criteria as supplementary studies or reviews.

A meta-analysis was not performed because the studies were judged to be too small and heterogeneous for meaningful quantitative synthesis.

Cohort studies or case series were identified in embryo and oocyte cryopreservation, ovarian tissue preservation, conservative surgical treatment of tumors, ovarian transposition (during radiotherapy), trachelectomy, sperm banking, rectal electroejaculation, hormonal manipulation, intracytoplasmic sperm injection, and testicular sperm extraction. Case reports were available for the other methods of fertility preservation.

Of the outcomes assessed, 111 studies reported on pregnancies, live births, or IVF outcome. Of these 111 studies, the majority were case series or case reports.
**Limitations of the Literature**

Review of the fertility preservation literature reveals a paucity of large and/or randomized studies. Most data come from cohort studies, case series, small nonrandomized clinical trials or case reports. Fertility preservation methods are still applied relatively infrequently in the cancer population, limiting greater knowledge about success and effects of different potential interventions. Other than risk of tumor recurrence, less attention is paid to the potential negative effects (physical and psychological) of fertility preservation attempts.

Little is known about the emotional impact of infertility or utilization of fertility preservation options on cohorts that are diverse in ethnicity and socioeconomic status, groups that face even greater barriers to fertility preservation.15,16

The Panel encourages additional well-designed studies evaluating methods of fertility preservation in people with cancer to help answer these questions. However, the Panel also notes that the traditional gold standard of randomized, controlled, and blinded therapeutic studies may not be possible in this area.

**I. Are Cancer Patients Interested in Fertility Preservation Interventions?**

The available evidence suggests that fertility preservation is of great importance to many people diagnosed with cancer, and that infertility resulting from cancer treatment may be associated with psychosocial distress. Although cancer survivors can become parents through options such as adoption and third-party reproduction (using gamete donation or a gestational carrier),17 most prefer to have a biological offspring, even if they have concerns about birth defects that could be caused if the parent had cancer treatment before conception or anxiety about their own longevity or their child’s lifetime cancer risk. One study in men suggested that having banked sperm was a positive factor in coping emotionally with cancer, even if samples were never used. Cancer survivors who are free of disease typically view themselves as healthy enough to be good parents, and in fact view their experience of illness as one that can enrich their parental role. Most put a higher value on family closeness after cancer and believe they are less bothered by daily stresses.19,20,23 It may be impossible for physicians to know how important fertility preservation is to their patients unless they ask, since many patients may not bring up the topic. A recent report by the President’s Cancer Panel recommends that all cancer patients of reproductive age be informed about the possibility of treatment-related infertility.18 Figure 1 and Table 3 provide guidance to oncologists in initial discussions.

Surveys of cancer survivors have identified an increased risk of emotional distress in those who become infertile because of their treatment.19,20,25-28 These studies mirror what has been observed in infertile noncancer populations where research clearly shows that long-term quality of life is affected by unresolved grief and depression, as well as reduced life satisfaction and increased anxiety. Some evidence suggests that patients may choose a less efficacious treatment strategy in order to avoid greater toxicity and long-term complications. For example, if given a choice, young women with early-stage breast cancer may choose a less toxic regimen of chemotherapy even if it confers slightly less protection from recurrence.27

Parents may also be interested in fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand, but potentially traumatic to them as adults. Use of established methods of fertility preservation (sperm cryopreservation and embryo freezing) in postpubertal minor children requires patient assent and parental consent. Unfortunately, the modalities that are available to prepubertal children to preserve their fertility are limited by patients’ sexual immaturity and are essentially experimental. Efforts to preserve fertility of children using experimental methods should only be attempted under institutional review board (IRB)–approved protocols, where proper attainment of informed consent from a legally authorized representative(s) (ie, parent[s] or guardian[s]) and of childhood assent can be ensured. It has been suggested that to overcome some of the practical obstacles involved in studying experimental fertility preservation in children, the consent process should be performed in two stages. The decision to harvest gametes would be made at the time of cancer treatment, and consent for the procedure would rely on parents/guardians. The decision of how to use the gametes after they have been isolated could be made at a future point by the patient. Therefore, the adult patient would be better able to express personal preferences about the handling of the tissue.

**II. What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Males?**

The Panel reviewed the available information supporting sperm cryopreservation, testicular hormonal suppression, and
testicular tissue cryopreservation. The available evidence suggests that sperm cryopreservation is an effective method of fertility preservation in males treated for cancer. In contrast, gonadoprotec-
tion through hormonal manipulation is ineffective. Testicular
tissue or spermatogonial cryopreservation and transplantation or
testis xenografting are in the early phases of experimentation and
have not yet been successfully tested in humans. Table 4 summa-
rizes the fertility preservation options in males. The Panel notes
that available interventions are unlikely to delay initiation of can-
ter treatment once a patient is successfully referred.

*Sperm cryopreservation.* Due to recent advances in IVF technol-
gy and sperm banking procedures, even men with extremely reduced
sperm count and motility are candidates for sperm cryopreservation.
It is strongly recommended that sperm be collected before initiation of
cancer therapy because the quality of the sample and sperm DNA
integrity may be compromised even after a single treatment ses-
sion. In addition, depending on the type of cancer—particularly
testicular cancer and Hodgkin’s lymphoma—and the overall condi-
tion of the patient, sperm quality may be poor even in patients who
have not yet started treatment. Many patients have to start
chemotherapy immediately or soon enough to limit the number of
ejaculates to one or two samples. Even in these instances, it is reason-
able to make every effort to bank sperm since recent progress in
andrology laboratories and in the use of assisted reproductive tech-
niques, particularly the technique of intracytoplasmic sperm injection
(ICS) allows the successful freezing and future use of a very limited
amount of sperm. There are case reports and small case series of
successful collection of sperm from a postmasturbation urine sample,
rectal electroejaculation under anesthesia, and testicular sperm
aspiration, but these are uncommon and/or investigational meth-
ods. Oncologists should make every effort to discuss sperm banking
with appropriate patients, though a recent survey suggests

### Table 3. Points of Discussion Between the Patient and Physician: Fertility Preservation Methods in Cancer Patients

- Cancer and cancer treatments vary in their likelihood of causing infertility. Individual factors such as disease, age, treatment type and dosages, and pre-
treatment fertility should be considered in counseling patients about the likelihood of infertility.
- Patients who are interested in fertility preservation should consider their options as soon as possible to maximize the likelihood of success. Some female
treatments are dependent upon phase of the menstrual cycle and can only be initiated at monthly intervals. Discussion with reproductive specialists and
review of available information from patient advocacy resources (for example, FertileHope, the Lance Armstrong Foundation/Livestrong, the Susan G.
Komen Breast Cancer Foundation) can facilitate decision-making and treatment planning.
- The two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for males and embryo freezing for females.
- Conservative surgical approaches and transposition of ovaries or gonadal shielding prior to radiation therapy may also preserve fertility in selected cancers.
- Data are very limited, but there appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and
pregnancy, even in hormonally sensitive tumors.
- Aside from hereditary genetic syndromes and in utero exposure to chemotherapy, there is no evidence that a history of cancer, cancer therapy, or fertility
interventions increase the risk of cancer or congenital abnormalities in the progeny.
- Treatment-related infertility may be associated with psychosocial distress, and early referral for counseling may be beneficial in moderately distressed people.

### Table 4. Summary of Fertility Preservation Options in Males

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Definition</th>
<th>Comment</th>
<th>Considerations</th>
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</thead>
<tbody>
<tr>
<td>Sperm cryopreservation (S) after masturbation</td>
<td>Freezing sperm obtained through masturbation</td>
<td>The most established technique for fertility preservation in men; large cohort studies in men with cancer</td>
<td>Outpatient procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Approximately $1,500 for three samples stored for 3 years, storage fee for additional years*</td>
</tr>
</tbody>
</table>
| Sperm cryopreservation (S) after alternative methods of sperm collection | Freezing sperm obtained through testicular aspiration or extraction, electroejaculation under sedation, or from a post-

masturbation urine sample | Small case series and case reports | Testicular sperm extraction-outpatient surgical procedure |
| Gonadal shielding during radiation therapy (S) | Use of shielding to reduce the dose of radiation delivered to the testes | Case series | Only possible with selected radiation fields and anatomy |
| | | | Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs |
| Testicular tissue cryopreservation | Freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation in animals | Has not been tested in humans; successful application in animal models | Outpatient surgical procedure |
| Testis xenografting | Spermatogonial isolation (I) | | |
| | Spermatogonial isolation (I) | Use of hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy | Studies do not support the effectiveness of this approach |

Abbreviations: S, standard; I, investigational.

*Costs are estimates.
that oncologists lack knowledge about recent advances in assisted reproductive techniques.

Sperm cryopreservation in boys and young men involves additional considerations. Spermatogenesis, the production of sperm, occurs at approximately 13 to 14 years, but once sperm are present, the patient’s age does not seem to affect quality of sperm produced.49 However, prepubertal boys have not yet developed gametes, and collection of semen through masturbation in adolescents may be compromised by embarrassment and issues of informed consent. For example, one study suggested adolescent boys may be more successful if a parent does not accompany them to the sperm bank.50

**Hormonal gonadoprotection.** The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients. Hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy is given,51,52 nor did it speed recovery of spermatogenesis in 18 men after nonsterilizing treatment compared to concurrent controls.53,54 Based on observations in rats, a small prospective study evaluated the effects of hypothalamic-pituitary-gonadal suppression plus testosterone in seven men rendered azoospermic after chemotherapy or radiation treatment for childhood cancer. No recovery of spermatogenesis was seen after 12 weeks of suppression.55 In contrast, a very small study evaluating testosterone in men without cancer treated with cyclophosphamide for glomerulonephritis suggested some benefit.56

**Other methods to preserve male fertility.** Other methods, such as testicular tissue cryopreservation and reimplantation57 or grafting of human testicular tissue to SCID mice to facilitate spermatogenesis,58,59 remain experimental and have not been tested in humans. Of note, such approaches are also the only methods of fertility preservation potentially available to prepubertal boys.

**Other considerations of fertility preservation options in males.** Epidemiological studies confirm that most young male patients with cancer are not referred for sperm banking.12,37,38 Reasons for this apparent underutilization are likely multifactorial. Physicians may not discuss or emphasize opportunities to preserve fertility before treatment.60 Psychological, logistic and financial constraints on patients may further limit sperm banking. Men may be traumatized about their diagnosis or lack interest in fertility preservation at the time of diagnosis. However, two recent surveys suggest that for men who desire future children, lack of timely information is the most common reason for not banking sperm.19,20 Responsibility for organizing an appointment with the cryopreservation laboratory often falls to the patient. Most insurance companies in the United States do not cover sperm cryopreservation. However, even in the United Kingdom, where the national health system subsidizes sperm banking for young cancer patients, many young men are not given referrals.

Even when sperm is banked, most studies suggest that a minority (up to 30%, but <10% in most cohorts) of men return to use their stored specimens.41,62-64 Storage fees are rarely a reason that men have cryopreserved semen destroyed.65

**Embryo cryopreservation.** Embryo cryopreservation is considered an established fertility preservation method as it has routinely been used for storing surplus embryos after in vitro fertilization for infertility treatment. This approach typically requires approximately two weeks of ovarian stimulation with daily injections of follicle-stimulating hormone from the onset of menses. Follicle development is monitored by serial ultrasounds and blood tests. At the appropriate time, an injection of HCG is administered to start the ovulatory cascade, and oocytes are subsequently collected by ultrasound guided transvaginal needle aspiration under intravenous sedation. Oocytes are fertilized in vitro and cryopreserved after fertilization. Because stimulation must be started at the onset of menses and takes two weeks, a delay of 2 to 6 weeks in chemotherapy initiation may be required if reproductive specialists do not see women early in their menstrual cycle. Most insurance companies do not offer assisted reproductive techniques as benefits so this approach may be associated with high out-of-pocket costs for most women. A partner or sperm donor is also required.

Live birth rates after embryo cryopreservation depend on the patient’s age and the total number of embryos cryopreserved and may be lower than with fresh embryos. Oocyte collection can be performed without ovarian stimulation ("natural cycle-IVF") but the embryo yield is extremely low.77,78 For women with hormone-sensitive tumors,79 alternative hormonal stimulation approaches such as letrozole or tamoxifen have been developed to theoretically reduce the potential risk of estrogen exposure. Short term breast cancer recurrence rates after ovarian stimulation using letrozole or tamoxifen concurrent with follicle stimulating hormone (FSH) administration have been compared to nonrandomized controls and no increase in
cancer recurrence rates has been noted in these initial studies.\textsuperscript{77,78} Only a small percentage of cancer survivors have yet returned to utilize their embryos but the initial pregnancy rates are encouraging.\textsuperscript{77,79} Nevertheless, long-term follow-up with a larger number of patients is needed to evaluate the safety and efficacy of this approach. The panel also notes that letrozole and tamoxifen should not be given to a woman after pregnancy is established.\textsuperscript{80,81} Recently, standard ovarian stimulation with coapplication of a progestin-releasing IUD has been reported to allow successful preservation of embryos in a patient with endometrial cancer.\textsuperscript{82}

\textbf{Oocyte cryopreservation.} Cryopreservation of unfertilized oocytes is another option for fertility preservation, particularly in patients for whom a partner is unavailable, or who have religious or ethical objections to embryo freezing. The oocytes are thawed later and fertilized in vitro. Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays in therapy and potential risks of short-term exposure to high hormonal levels. As with embryo cryopreservation, letrozole or tamoxifen can be used. Research indicates that unfertilized oocytes are more prone to damage during cryopreservation procedures than embryos, and as a result, the overall pregnancy rates may be lower than standard IVF procedures.\textsuperscript{83} There have been approximately 120 deliveries with this approach,\textsuperscript{83} and efforts to improve the efficiency of cryopreservation may increase success rates.\textsuperscript{84,85} Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency

\begin{table}[h]
\centering
\caption{Fertility Preservation Options in Females}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Intervention} & \textbf{Definition} & \textbf{Comment} & \textbf{Considerations}\tabularnewline
\hline
Embryo cryopreservation (S) & Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation & The most established technique for fertility preservation in women & \begin{itemize}
\item Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle
\item Outpatient surgical procedure
\item Requires partner or donor sperm
\item Approximately $8,000 per cycle, $350 per year storage fees
\end{itemize}\tabularnewline
\hline
Oocyte cryopreservation (I) & Harvesting and freezing of unfertilized eggs & Small case series and case reports; as of 2005, 120 deliveries reported, approximately 2% live births per thawed oocyte (3-4 times lower than standard IVF) & \begin{itemize}
\item Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle
\item Outpatient surgical procedure
\item Approximately $8,000 per cycle, $350/yr storage fees
\end{itemize}\tabularnewline
\hline
Ovarian cryopreservation and transplantation (I) & Freezing of ovarian tissue and reimplantation after cancer treatment & Case reports; as of 2005, two live births reported & \begin{itemize}
\item Not suitable when risk of ovarian involvement is high
\item Same day outpatient surgical procedure
\end{itemize}\tabularnewline
\hline
Gonadal shielding during radiation therapy (S) & Use of shielding to reduce the dose of radiation delivered to the reproductive organs & Case series & \begin{itemize}
\item Only possible with selected radiation fields and anatomy
\item Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs
\end{itemize}\tabularnewline
\hline
Ovarian transposition (oophoropexy) (S) & Surgical repositioning of ovaries away from the radiation field & Large cohort studies and case series suggest approximately 50% chance of success due to altered ovarian blood flow and scattered radiation & Same day outpatient surgical procedure\tabularnewline
\hline
Tracheectomy (S) & Surgical removal of the cervix while preserving the uterus & Large case series and case reports & \begin{itemize}
\item Inpatient surgical procedure
\item Limited to early stage cervical cancer; no evidence of higher cancer relapse rate in appropriate candidates
\item Expertise may not be widely available
\end{itemize}\tabularnewline
\hline
Other conservative gynecologic surgery (S/I) & Minimization of normal tissue resection & Large case series and case reports & \begin{itemize}
\item Expertise may not be widely available
\end{itemize}\tabularnewline
\hline
Ovarian suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists (I) & Use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy & Small randomized studies and case series. Larger randomized trials in progress & \begin{itemize}
\item Medication given before and during treatment with chemotherapy
\item Approximately $500/mo
\end{itemize}\tabularnewline
\hline
\end{tabular}
\end{table}

Abbreviations: S, standard; I, investigational.
*Costs are estimates
Ovarian transplant procedure was reported in 2000. Ovarian tissue cryopreservation has been performed in humans for less than a decade, and the first chemotherapy treatments have been administered.

Large randomized clinical studies of ovarian suppression may help preserve ovarian function when given during chemotherapy. The combination of GnRH agonists and oral contraceptives to preserve fertility in women treated for advanced Hodgkin’s lymphoma.

Anecdotally, because GnRH analogs are readily available, this strategy has been used widely without clear evidence for efficacy or full understanding of the potential risks and benefits, especially in women with hormone-sensitive tumors. At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials.

Ovarian transposition. Ovarian transposition (oophorectomy — surgically moving ovaries as far as possible from the radiation field) can be offered when pelvic radiation is used for cancer treatment. The procedure can be done laparoscopically if laparotomy is not needed for the primary treatment of the tumor. Because of the risk of remigration of the ovaries, this procedure should be performed as close to the radiation treatment as possible. The overall success rate as judged by preservation of short-term menstrual function is approximately 50%. Scattered radiation and alteration of ovarian blood supply appear to be the main reasons behind the failures. Total radiation dose and the dose received by the “less-irradiated” ovary also affect the outcome.

Ovarian repositioning may not always be needed to restore fertility, as spontaneous pregnancies have been reported in women with transposed ovaries. If infertility develops and in vitro fertilization is needed after ovarian transposition however, the performance of oocyte retrieval becomes more complicated. In this case, either a second procedure is needed to reposition the ovaries to the pelvis, or egg collection will have to be performed percutaneously with the risk of reducing the efficiency of this procedure.

Other risks include ovarian dysfunction leading to ovarian cysts and the theoretical risk of increased difficulty diagnosing ovarian cancer if the ovaries are no longer palpable on bimanual examination.

Conservative gynecologic surgery. It has been estimated that nearly 50% of patients with cervical carcinoma under the age of 40 are eligible for radical trachelectomy, a procedure in which the cervix is resected but the uterus is spared. The procedure is typically performed vaginally with laparoscopic assistance, but an abdominal variant has also been described. It has been suggested that the procedure be restricted to stage IA2-IB disease with less than 2 cm in diameter and less than 10 mm invasion. The recurrence rates following radical trachelectomy appear to be similar to that of radical hysterectomy but no randomized study exists.

To date, at least 236 women underwent the procedure with 63 live births resulting. There is an increased risk in midtrimester losses and preterm birth. There is also a higher incidence of infertility due to cervical abnormalities, which would require the use of assisted reproduction technologies.

In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery and/or lower dose chemotherapy with the intent of sparing the...
reproductive organs as much as possible for subsequent fertility. Reports are generally limited in size and lack randomized controls. However, they reveal no obvious increased risk of disease recurrence in women treated with fertility sparing approaches. For example, in the two largest published series of 212 women with malignant ovarian germ cell tumors, fertility-sparing surgery with or without chemotherapy did not appear to substantially affect the risk of recurrence compared with historical controls.124,125

Other considerations of fertility preservation options in females. The possibility that fertility preservation interventions and/or subsequent pregnancy may increase the risk of cancer recurrence has been most concerning in breast cancer and the gynecologic malignancies. To date, the effect of subsequent pregnancy after breast cancer on prognosis has not been studied prospectively.126 Several case-control and retrospective cohort studies have not shown a decrement in survival or an increase in risk of recurrence with pregnancy.127-133 While these data are reassuring, the studies are all limited by significant biases, and concerns remain for some women and their physicians.20,134 Since breast, endometrial, and ovarian cancer cells have been shown to express GnRH receptors, a GnRH agonist could affect cancer cell proliferation or apoptosis.135 However, GnRH agonists have also been used as treatments for hormone receptor-positive premenopausal breast tumors, and combined trials of GnRH agonists and chemotherapy are underway.136 In women with hormone receptor–positive breast cancer who undergo successful fertility preservation treatments, continued menstrual cycling after chemotherapy could theoretically increase relapse rates by interfering with one proposed mechanism of action (ovarian suppression) of adjuvant therapy.137

There is concern that instrumentation of the pelvis to perform fertility preservation maneuvers can result in local spread of disease. In one case report, a woman with cervical adenocarcinoma developed an abdominal wall metastasis at the site of trocar insertion for laparoscopy done for ovarian transposition for fertility preservation.138 It is unclear how often this occurs however.

IV. What Is the Role of the Oncologist in Advising Patients About Fertility Preservation Options?

Discuss infertility as a potential risk of therapy. As with the other potential complications of cancer treatment, oncologists have a responsibility to inform patients about the risks that their cancer treatment will permanently impair fertility. Yet, recent surveys of male and female cancer survivors of reproductive age concur that at least half have no memory of a discussion of fertility at the time of their treatment disposition.19,20,23,139 The few studies of oncologists’ practices of discussing infertility confirm patients’ reports. In clinical practice many oncologists do not mention even proven techniques such as sperm banking.48,140,141 Even when patients do recall infertility discussions, many are dissatisfied with the quality and amount of information provided.27,141,142 Almost all these studies rely on retrospective self-reports from either oncologists or cancer survivors, and the role of recall bias cannot be ascertained. Patients who participate in survey research are usually self-selected, affluent, well-educated, Caucasians.19,20 Furthermore, the participation rates by physicians have been very low, often under 33%, so that it is unclear whether the results are generalizable.48,141

Studies document many reasons why oncologists do not discuss infertility with the frequency that they discuss other treatment related complications such as neutropenia and cardiopulmonary toxicity. Physicians may be prioritizing discussions about immediate or potentially life-threatening complications instead of discussing infertility. Data regarding the risks of infertility with various chemotherapy regimens are poor or nonexistent. Some physicians do not recognize the importance of fertility to cancer survivors142 or believe that the cost of fertility preservation interventions is prohibitive. For example, 51% of oncologists in a United States study believed that most men could not afford to bank sperm because of out-of-pocket costs.143 However, oncologists overestimated these costs48 and their deterrent effect; in a companion survey of young men, only 7% cited financial reasons for not banking sperm.19 Oncologists are also less likely to refer patients for sperm banking if the cancer prognosis is poor141,144 or they believe that patients would not be interested for other reasons. Physicians’ emotional discomfort with discussing fertility issues may also play a role141 along with lack of knowledge and time. While the Panel recommends discussion about risks of treatment-induced infertility at the earliest possible opportunity, the Panel recognizes that raising this issue at the first encounter or at the time of diagnosis may not always be practical or wise. Clinician judgment should be employed in the timing of raising this issue, with the goal of discussion and referral at the earliest possible opportunity.

While professional organizations such as the American Society for Reproductive Medicine and patient advocacy organizations such as Fertile Hope,145 Lance Armstrong Foundation/Livestrong, and the Susan G. Komen Breast Cancer Foundation do provide patient information, patients may not be aware of these resources and able to access information in a timely fashion when confronted with a new diagnosis of cancer. In addition, a physician’s recommendation is a very strong predictor of whether a man banks sperm, almost as influential as the patient’s desire for children in the future.19,146 This finding is reminiscent of the important influence of physician recommendations in promoting smoking cessation and cancer screening147,148 and suggests that physician encouragement affects patient interest in fertility preservation options. An algorithm for triaging fertility preservation referrals is presented in Figure 1, and suggested talking points are illustrated in Table 3. Ideally, after referral, the decision about who is an appropriate candidate to attempt specific fertility preservation techniques could be rendered by a team including a medical oncologist, reproductive endocrinologist, and a psychosocial provider, all guided by written protocols which can be shared with patients.149 Patients, and parents of minors, should not be provided with unrealistic expectations about their cancer prognoses, the success rates of fertility preservation interventions or the cost of attempting to preserve fertility, and the option of declining fertility preservation interventions should also be discussed. Potential legal issues, such as ownership of embryos and reproductive tissue in the event of a patient’s death, divorce or incapacity, should also be discussed by the reproductive specialist.

Answer basic questions about whether fertility preservation options decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring. Specific risks of fertility preservation options are discussed above in the sections on male and female considerations. Although studies are generally small and either not prospective or have short follow-up, there is no evidence that currently used fertility preservation options directly compromise the success of cancer therapy. There may of course be individual considerations, such as if chemotherapy is delayed to give time to pursue fertility preservation options or in the case of hormonally sensitive tumors.
There have been many published reports regarding parental outcome after interventions to spare fertility through cancer treatment and/or pregnancy following cancer. However, available studies are generally limited to case reports and small series. The few larger studies addressing these issues have generally been comprised of heterogeneous patient populations, retrospective in nature, with relatively short-term follow-up, and lacking randomized controls. Available data are reassuring, however, in that there is no clear increased risk to a survivor’s health from available interventions to preserve fertility or from subsequent pregnancy, beyond that of normal populations with similar comorbidities.

In light of the long-term organ toxicity that may result from cancer and cancer therapy, pregnancy after cancer treatment may be complicated by an increased risk of organ impairment, especially of the heart, lungs, and uterus. For example, there is evidence that pregnancy may increase the risk of worsening cardiac ejection fraction in women treated with doxorubicin for childhood cancer, and uterine or total-body irradiation appears to increase the risk of miscarriage, prematurity and low birth weight. While several studies have revealed no evidence that use of cryopreserved sperm regardless of mode of extraction or fertilization technique has a detrimental effect on perinatal health of offspring or mother, the available data regarding the effects of female fertility sparing interventions on maternal or fetal perinatal health are limited. The major risk that has been recognized appears to be an increased risk of cervical incompetence, miscarriage, prematurity and low birth weight in women with lower gynecologic malignancies who have undergone conservative surgery such as trachelectomy for fertility preservation, and the health risks associated with a higher rate of multiple births after assisted reproductive technology. Short and long-term follow-up following fertility sparing interventions for women with cancer is warranted. At the present time, in light of concerns, women with a history of cancer and cancer treatment should be considered high risk for perinatal complications and would be prudent to seek specialized perinatal care.

Aside from hereditary genetic syndromes, however, there is scant evidence that a history of cancer, cancer therapy, or fertility interventions increases the risk of problems in the progeny. Available studies including large registry studies have revealed no increased risk of genetic abnormalities, birth defects, or cancers, aside from hereditary syndromes, in the children of cancer survivors. Data regarding the effects of interventions to spare parental fertility on the health of the progeny are limited to case reports and small series with relatively short follow-up. At present, there does not appear to be a clear detrimental effect from any of the available fertility sparing interventions. However, patients should be encouraged to participate in registries and clinical studies as available to define further the safety of fertility preservation interventions and strategies. As needed, refer patients to reproductive specialists and psychosocial providers. Oncologists should refer interested and appropriate patients to reproductive specialists as soon as possible. Some methods of fertility preservation in females require timing with the menstrual cycle, so expeditious referrals are suggested to avoid missing opportunities. As long as the oncologist presents the options in enough detail for the patient to decide whether to seek a consultation, the detailed counseling could be done by an infertility specialist. However, oncologists’ input will still be invaluable to help guide patients as they think about how to prioritize fertility preservation in the context of their cancer treatment plan. When referring patients, oncologists should remember that many methods are still investigational. Ethical guidelines published by the American Society for Reproductive Medicine states that fertility preservation involving oocyte, ovarian and testicular harvesting for freezing should be performed only in specialized centers working with IRB-approved consents. In addition, the experience of the infertility specialist in working with cancer patients should also be considered.

One option the oncologist should routinely offer is a referral for psychological counseling when a man or woman has moderate to severe distress about potential infertility. Research on infertility patients has shown that structured, cognitive-behavioral counseling can reduce anxiety and depression. The American Society for Reproductive Medicine has both a Fertility Preservation Special Interest Group (http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/fpsig/fpsig_index.html) and a Mental Health Professional Group (http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/MHPG/index.html).

Previous Consensus Statements

Consensus statements have also been developed by some professional societies, including the British Fertility Society (http://www.britishfertilitysociety.org.uk/practicepolicy/documents/fccpaper.pdf), the European Society of Human Reproduction and Embryology (ESHRE) Task Force (http://www.eshre.com), and the American Society for Reproductive Medicine. The Panel has evaluated the Guidelines produced by reproductive specialist societies and found them to be consistent with the ASCO guidelines.

Interpretive Summary

Fertility preservation is often possible in people undergoing treatment for cancer. Broader application of fertility preservation methods is limited by several factors: lack of knowledge about the risk of infertility with current cancer treatments, failure to discuss and consider options before treatment, lack of insurance coverage for most procedures with consequent high out of pocket costs, and the investigational status of many fertility preservation methods. The Panel recommends that oncologists discuss at the earliest opportunity the possibility of infertility as a risk of cancer treatment, recognizing that in many cases, adequate data are not available to provide accurate predictions for any one individual. For patients at risk for infertility who are interested in evaluating their options for fertility preservation, referral to appropriate specialists as early as possible is recommended. People attempting fertility preservation in the context of cancer treatment are encouraged to enroll in clinical trials that will advance the state of knowledge. Figure 1 and Table 3 provide additional guidance to oncologists in initial discussions. Supplementary materials available for public use such as a summary of guidelines, slide set, and patient information may be found on ASCO’s Web site (http://www.asco.org).

80. Tiboni GM: Aromatase inhibitors and terato-
genesis. Fertil Steril 81: 1189-1198, 2004


83. Oktay K, Ci AF, Bang H: The efficacy of oocyte cryopreservation in FSH-stimulated pressal


89. Oktay K: Evidence for limiting ovarian tissue harvesting for the purpose of transplantation to women younger than 40 years of age. J Clin Endo-
crinol Metab 87:1907-1908, 2002


91. Donnez J, Dolmans MM, Demyde D, et al: Live birth after orthotopic transplantation of cryopre-
served ovarian tissue. Lancet 364:1405-1410, 2004


94. Tryde Schmidt KL, Yding Andersen C, Starup J, et al: Orthotopic autotransplantation of cryopre-
served ovarian tissue to a woman cured of cancer- folic acid, growth factors, steroid production and oocyte re-
trieval. Reprod Biomed Online 8:448-453, 2004


crine function and oocyte retrieval after autologous transplantation of ovarian cortical strips to the forearm. JAMA 286:1490-1493, 2001

97. Oktay K, Buyuk E, Veeck L, et al: Embryo development after heterotopic transplantation of cryopre-
served ovarian tissue. Lancet 363:837-840, 2004


99. Kim SS, Radford J, Harris M, et al: Ovarian tissue harvested from lymphoma patients to pre-
serve fertility may be safe for autotransplantation. Hum Reprod 16:2028-2031, 2001


tion of irreversible oogenesis in chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotropin-releasing hormone agonist in parallel to chemotherapy. Hum Reprod 11:1620-1626, 1996

103. Fox KR, Scialla J, Moore H: Preventing chemotherapy-associated amenorrhea (CRA) with letrozole during adjuvant chemotherapy for early-

104. Recchia F, Sica G, De Filippi S, et al: Goserelin as ovarian protection in the adjuvant treat-

duced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral con-


roscopic unilateral ovarian transposition prior to ira-
diation: Prospective study of 20 cases. Cancer 77: 2638-2645, 1996

ocol Oncol 17:177-182, 1996


111. Darnwood MD, Hesla HS, Lowen M, et al: Induction of ovulation and pregnancy following lat-

position, pelvic irradiation and hysterectomy. J Re-
prod Med 49:573-574, 2004


115. Sonoda Y, Abu-Rustum NR, Gemignani ML, et al: A fertility-sparing alternative to radical hyster-
eyctomy: How many patients may be eligible? Gy-
 necol Oncol 95:534-538, 2004

369, 2005

ment to preserve the fertility of cervical carcinoma patients. Cancer 88:1077-1085, 2001

cases and review of the literature. Gynecol Oncol 94:614-623, 2004

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<td>Stephanie J. Lee*</td>
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<td>Pasquale Patrizio*</td>
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<td>W. Hamish Wallace*</td>
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<td>Lindsay N. Beck</td>
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<td>Fertile Hope (B)</td>
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<td>Lawrence V. Brennan*</td>
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Dollar Amount Codes: (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

*No significant financial relationships to disclose.

Author Contributions

Conception and design: Stephanie J. Lee, Kutluk Oktay
Administrative support: Karen Hagerty
Collection and assembly of data: Karen Hagerty
Data analysis and interpretation: Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Lindsay N. Beck, Lawrence V. Brennan, Kutluk Oktay
Final approval of manuscript: Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Lindsay N. Beck, Lawrence V. Brennan, Kutluk Oktay
ERRATA

The June 20, 2006, ASCO special article by Lee et al entitled, “American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients” (J Clin Oncol 24:2917-2931, 2006) contained an error. In Table 1, the dosage for busulfan was given as 600 mg/kg, while it should have been 600 mg/m². This was due to a misprint in the original textbook where the data were taken.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.904


In the Introduction section, the third sentence of the first paragraph was given as:

“Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% v 33.3%, respectively; \( P = .008 \)),³ mitomycin plus vinblastine (30.0% v 11.6%, respectively; \( P < .0001 \)),⁴ or methotrexate plus fluorouracil (42% v 21%, respectively; \( P < .001 \))⁵ but not compared with fluorouracil plus vinorelbine (38.9% v 43.0%, respectively; \( P = .69 \))⁶ and paclitaxel (25.0% v 32.0%, respectively; \( P = .1 \)).⁷”

While it should have read:

“Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% v 33.3%, respectively; \( P = .008 \)),³ mitomycin plus vinblastine (30.0% v 11.6%, respectively; \( P < .0001 \)),⁴ or methotrexate plus fluorouracil (42% v 21%, respectively; \( P < .001 \))⁵ but not compared with fluorouracil plus vinorelbine (43.0% v 38.9%, respectively; \( P = .69 \))⁶ and paclitaxel (32.0% v 25.0%, respectively; \( P = .1 \)).⁷”

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.905