Skin-Sparing Mastectomy

Specialty Bias and Worldwide Lack of Consensus

Skin-sparing mastectomy (SSM) tends to be confined to multidisciplinary practices within designated breast units. Mastectomy and immediate breast reconstruction usually are undertaken either as a joint procedure between a general and plastic surgeon or exclusively by a dedicated breast surgeon with “oncoplastic” training. This may in part account for the “patchy” and variable nature of the responses in the survey conducted by Bleicher et al.,¹ as dissemination of the technique throughout the global breast carcinoma community continues.

SSM represents the latest phase in the development of progressively less mutilating forms of mastectomy for breast carcinoma treatment, with early Halstedian procedures removing much of the breast skin envelope.² However, to my knowledge, the oncologic equivalence of SSM to conventional modified radical mastectomy has never been validated in prospective controlled trials. Undoubtedly, patient demand has influenced surgical practice, and transatlantic differences with regard to familiarity and knowledge of SSM techniques are evident. Some individuals felt sufficiently confident to complete the survey, yet displayed a fundamental flaw in their knowledge of reconstructive options within the context of SSM. It is reassuring that nearly 90% of surgical oncologists were familiar with the literature base for SSM, although levels of skepticism exist that are inversely related to the degree of surgical involvement in the SSM procedure itself. The authors allude to the dominance of plastic surgery journals as a vehicle for the publication of articles on SSM despite two of the seminal works on this subject appearing in cancer journals (one of which has a breast surgeon as the first author)³,⁴

The precise patterns of incision and the extent of skin resection must be tailored to individual cases. There is a risk of oncologic compromise when standard incisions are adopted in a blanket manner or when general surgeons are coerced into performing “pure” skin-sparing resections when these are inappropriate. Plastic surgery colleagues must respect oncologic mandates and be prepared to sacrifice additional native breast skin when indicated. Increasing numbers of patients are receiving postmastectomy radiotherapy and the Survey by Bleicher et al.¹ revealed that nearly half of radiation oncologists would be “more aggressive” with radiotherapy regimens after SSM techniques. This may have implications for patients with implant-based reconstructions, for whom hypofractionated dosage has been employed to minimize capsular contracture. Long-term data regarding rates of loco-regional recurrence and distant recurrence will clarify relative indications for SSM, but in the interim, patient selection criteria and quality control issues must be scrutinized constantly and subjected to ongoing audit and evaluation.⁵
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It is entirely correct that, by surgical standards, skin-sparing mastectomy (SSM) is a relatively new technique utilized predominantly by those with an interest and subspecialization in breast surgery. Our results confirmed this indirectly by virtue of the trends observed correlating increasing surgical and breast focus with decreasing skepticism of the procedure.1

Dr. Benson is also wise to note that although guidelines for resection exist, patient treatment must be tailored individually, and adherence to guidelines or surgical definitions is not a valid rationale for compromising oncologic safety. Variation from these guidelines is not only appropriate but mandatory in instances in which patient outcome may be better optimized as a result. Nonetheless, the literature does provide such a definition,1 which serves as a framework for SSM from which to base treatment decisions, and our survey was designed to assess knowledge of that definition.

We also agree that until a randomized trial is conducted, SSM may continue to be the subject of controversy, despite the growing empiric data reported to date. However, the more likely candidate for a clinical trial, which may propel the evolution of the mastectomy, is evaluation of nipple-areola complex-sparing mastectomies, which are just now beginning to undergo feasibility and safety evaluations. Such a trial would surely be based on the empiric skin-sparing evidence garnered to date, as well as prior investigations into nipple-areola complex involvement.2,3

As breast treatment continues to evolve, surgeons must be willing to adapt to and embrace such change, regardless of whether those changes are patient driven or brought about by advances in laboratory science.

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Relation between the Duration of Remission and Hyperglycemia during Induction Chemotherapy for Acute Lymphoblastic Leukemia with a Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone/Methotrexate-Cytarabine Regimen

We read with interest the recent article by Weiser et al.1 They conducted a trial in patients with acute lymphocytic leukemia who were treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) to delineate the impact of hyperglycemia on patient outcome. Hy-
perglycemia was found to occur in 37% of the patients. The patients who experienced hyperglycemia were found to have a shorter duration of complete remission compared with those patients without hyperglycemia. Patients with hyperglycemia also were found to have a shorter median overall survival, and they were more likely to develop sepsis and complicated infections. Weiser et al. also found hyperglycemia to be an independent risk factor for early disease recurrence and mortality on Cox regression analysis. However, we have a comment on the study.

Corticosteroids are widely employed in the treatment of patients with cancer, especially those with lymphoid malignancies. Therefore, hyperglycemia is not an uncommon clinical occurrence during chemotherapy, as in the study by Weiser et al. In the case of hyperglycemia, the dose of corticosteroid usually is reduced or withdrawn from the treatment. The role of the relative dose intensity of the drugs used in the treatment was not discussed in the study by Weiser et al. Is hyperglycemia an independent risk factor based on the relative dose intensity of the drugs used in the treatment? Is there any difference with regard to the relative dose intensity between the patients with hyperglycemia and those without hyperglycemia, although the toxicity was not found to be different in hyperglycemic patients compared with those who were normoglycemic (most likely an indirect indicator of relative dose intensity)? The relative dose intensity should be included in analyses. Therefore, it is difficult to state with certainty that hyperglycemia is an independent risk factor in patients with acute lymphoblastic leukemia without incorporating the relative dose intensity in the analysis.

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High-Dose Calcitriol, Zoledronate, and Dexamethasone for the Treatment of Progressive Prostate Carcinoma

We read with great interest the recent article by Morris et al. In their Phase I study of calcitriol, they found that pulsed calcitriol was well tolerated at doses ≤ 30 μg per day administered 3 times per week in combination with zoledronate, but they did not observe any significant activity in patients with advanced prostate carcinoma. They did not recommend Phase II studies due to difficulties associated with the scheduling of doses and due to the lack of significant activity in patients with advanced prostate carcinoma.

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We propose that the observed lack of activity may be related to the use of calcitriol and zoledronate in combination with each other. Most osteotropic factors, such as parathyroid hormone, 1,25-dihydroxyvitamin D3, and prostaglandins, induce the formation of osteoclasts by increasing the expression of the receptor activator of nuclear factor-κB ligand (RANKL) on bone marrow stromal cells and osteoblasts rather than by acting directly on osteoclast precursors; in this setting, it is RANKL that acts directly on osteoclast precursors to induce osteoclast formation and bone resorption. The process of bone resorption releases factors such as transforming growth factor beta, insulin-like growth factors, fibroblast growth factors, platelet-derived growth factor, and bone morphogenetic proteins, which stimulate the production of parathyroid hormone–related peptide by tumor cells as well as the production of factors that enhance tumor growth. This symbiotic relation between bone destruction and tumor growth leads to further increases in bone destruction and tumor growth. Increased bone resorption also occurs in osteoblastic prostate carcinoma lesions, and agents that block bone resorption (such as zoledronate) can decrease bone pain and the risk of pathologic fractures.

In vitro studies indicated that zoledronic acid exerted direct antitumor effects by inducing apoptosis, inhibiting cell adhesion molecules, preventing prostate and breast carcinoma cell adherence to bone, reducing interleukin-6 secretion from myelomatous stromal cells, and affecting angiogenesis. Thus, calcitriol (1,25-dihydroxycholecalciferol) itself may induce bone resorption and cause tumor regrowth, thereby counteracting the effectiveness of zoledronate against bone resorption and against prostate carcinoma cells metastasized to bone in patients with advanced-stage disease.

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D r. Altundag and colleagues suggest that the disappointing clinical results in our trial of high-dose calcitriol and zoledronic acid may be attributable to interactions between these two agents. They suggest that osteotropic factors such as 1,25-dihydroxyvitamin D3 increase bone resorption, which leads to the release of factors that stimulate tumor growth, and counteract the potential benefits conferred by the antosteoclastic and antitumor properties of zoledronate.

The assumptions on which this scenario is based are tenuous. Zoledronic acid is a powerful antiresorptive agent that is directly toxic to osteoclasts and induces osteoclast apoptosis. We know of no data to suggest that calcitriol inhibits the antiresorptive activity of zoledronate. In fact, bisphosphonates are highly active in calcitriol-induced hypercalcemia in thyro-parathyroidectomized animals. It was these very models that were used to develop zoledronate and compare its potency with that of pamidronate. Based on markers of bone resorption, it is difficult to interpret the interaction of calcitriol and zoledronic acid in our study. In terms of N-telopeptide levels, the 6 patients who received single-agent calcitriol experienced a mean increase of 42% by Week 5, although one of these patients exhibited a decrease of 37%. In contrast, patients who received calcitriol and zoledronic acid
had a mean decrease of 26% in N-telopeptide levels, suggesting that zoledronate inhibited bone resorption, albeit at a lower rate than one might anticipate.

In vitro evidence suggests that bisphosphonates can induce cytostasis and can reduce the invasiveness of prostate carcinoma cell lines,\(^1\)\(^2\) but even the investigators who performed the experiments that yielded this evidence question whether equivalent concentrations at the site of disease are achievable in routine clinical practice.\(^4\) A more relevant finding is that zoledronic acid appears to have no impact on PSA kinetics relative to placebo in humans, casting doubt on the hypothesis that zoledronic acid has clinically significant direct antitumor activity.\(^5\)

Finally, if calcitriol fuels tumor growth, one would expect accelerated growth in trials using calcitriol as a single agent, an outcome that has not been observed to date. More plausible reasons for the disappointing clinical results associated with our regimen are that zoledronate does not have demonstrable direct antitumor effects in humans and that the antitumor effects of single-agent calcitriol are modest at best, even when this agent is administered at escalated doses.

REFERENCES


