Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer

During the past half a century, a series of progressive, large-scale, randomised controlled trials have incrementally and steadily improved survival for women with breast cancer. Notably, all of them have built on modest gains and, in many cases, it has taken well done meta-analyses to fully define the advantages of these treatments. Meta-analyses of multiple studies have convincingly shown that bisphosphonates reduce skeletal events, whether caused by loss of bone density or breast cancer involvement. These analyses have also shown a significant survival advantage with the addition of these agents.[1]

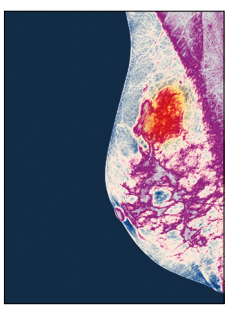
In *The Lancet Oncology*, Michael Gnant and colleagues[2] provide additional data from ABCSG-18, a randomised trial of denosumab in postmenopausal women with hormone receptor-positive breast cancer. A previous report on this trial documented a significant decrease in skeletal-related events with denosumab,[3] and the current report[2] provides convincing evidence that adjuvant denosumab also improves disease-free survival (hazard ratio 0·82 [95% CI 0·69–0·98], Cox p=0·0260). Furthermore, the addition of adjuvant denosumab to the regimen did not increase toxic effects—most notably, there were no documented cases of osteonecrosis of the jaw.

These are practice-changing results, and clearly establish denosumab as a reasonable alternative to bisphosphonates. The results also strongly support the inclusion of some form of bone agent in addition to standard-of-care adjuvant therapy for hormone receptor-positive breast cancer in postmenopausal patients.

However, many crucial questions remain unanswered. Foremost is the continued lack of understanding of how denosumab or bisphosphonates favourably affect disease-free survival, and particularly recurrences at sites other than bone.[4] Studies have shown that about a third of women undergoing treatment for early-stage invasive breast cancer have breast cancer cells detectable in their bone marrow when sampled with 5–10 mL of aspirated marrow, and these cells persist in the marrow 1 year later.[5] This finding, given the small amount of marrow sampled, implies that far more patients actually have breast cancer cells in their bone marrow than we realise. Conceivably, although these cells can escape from the breast, they might be in some way incompetent to grow into metastases. Alternatively, an as yet poorly defined concept of dormancy might limit their potential for growth. Another possibility is that these cells are kept under control by immunological surveillance until some future stressor (such as development of depression, central obesity, or diabetes) affects the ability of the host to eliminate this small tumour burden, and metastases consequently appear. Some researchers have argued that these breast cancer cells in the marrow are one step in a process that leads to metastases at other sites, rather than through random seeding to different organs. Bone marrow is clearly a preferred site of breast cancer seeding and growth because most women who die from breast cancer will have bone metastases at the time of death, although a substantial proportion of women with metastatic disease have predominantly visceral metastases.

A second unanswered question regards the observation that a delay in initiating denosumab therapy was apparently associated with a diminished disease-free survival benefit. Similar findings have also been shown for bisphosphonates.[6] Studies dating back several decades showed that brief perioperative chemotherapy with cyclophosphamide reduced recurrence, suggesting that there might be some sort of window of opportunity for affecting disseminated breast cancer cells, which is lost over several months. This time constraint is a major potential issue, especially in the USA, where unsatisfying and time-consuming struggles between insurers and physicians (or their institutions) delay approvals for bone agents in the adjuvant setting.

A third unanswered question is why the success of these approaches is limited to hormone receptor-positive breast cancer. One possible explanation is related to the fact that hormone receptor-positive breast cancers continue to recur in a linear fashion for at least 30 years after diagnosis, implying that these women must have breast cancer cells within their marrow that survive treatment and are responsible for eventual relapse. By contrast, in hormone receptor-negative breast cancer, which initially has a higher rate of relapse than does



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hormone receptor-positive cancer, the survival curves flatten out. Thus, compared with patients with hormone receptor-positive breast cancer, those with hormone receptor-negative disease might actually have fewer breast cancer cells persistent in their marrow that can be affected by bisphosphonate or denosumab therapy.

This study of denosumab, in addition to many randomised controlled trials of bisphosphonates, indicates that adjuvant dosing with these therapies is generally safe, leads to a substantial reduction in skeletal events and an improvement in disease-free survival, and should be part of almost all adjuvant regimens for postmenopausal hormone receptor-positive breast cancer.

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I declare no competing interests.

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