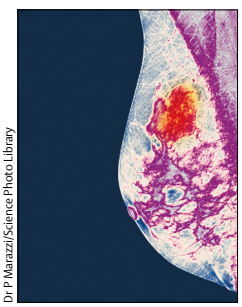
Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer



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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

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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Hypofractionated radiotherapy after mastectomy: a new frontier

Hypofractionation is an elegant approach that promises to help to contain the costs of cancer care and mitigate financial toxicity. For selected patients with breast cancer, considerable evidence from large randomised trials with long follow-up, primarily in the setting of breast conservation, supports the equivalent efficacy and toxicity of shorter courses of hypofractionated whole-breast radiotherapy (such as 42·5 Gy in 16 fractions[1] or 40 Gy in 15 fractions[2]) than conventional courses, which required 5 or more weeks of daily treatments. The transformative impact of hypofractionation in the setting of breast conservation[3] has also motivated investigation of hypofractionation after mastectomy.[4] In *The Lancet Oncology*, Shu-Lian Wang and colleagues[5] report the 5-year outcomes of a randomised, non-inferiority, open-label, phase 3 trial in China that compared postmastectomy hypofractionated radiotherapy (43·5 Gy in 15 fractions over 3 weeks) with conventional treatment (50 Gy in 25 fractions over 5 weeks).

One reason that trials are needed specifically in patients who have undergone mastectomy relates to the more advanced stage of patients typically treated with postmastectomy radiotherapy. In the trial by Wang and colleagues, eligibility criteria included at least four positive lymph nodes or T3–4 tumours. Although the radiobiological properties of the individual cells causing these tumours might not necessarily be expected to diverge from those in patients with earlier stages of the disease, who constituted the bulk of patients enrolled in clinical trials establishing hypofractionation after breast-conserving surgery, the number of tumour clonogens remaining after surgery and systemic therapy in the breast or regional nodal basins might be higher in patients such as those enrolled in the trial by Wang and colleagues than in those with early-stage disease. In this context, the fact that no difference in 5-year cumulative incidence of locoregional recurrence was observed is reassuring (8·3% [90% CI 5·8–10·7] in the hypofractionated radiotherapy group *vs* 8·1% [90% CI 5·4–10·6] in the conventional fractionated radiotherapy group; absolute difference 0·2%, 90% CI –3·0 to 2·6; hazard ratio 1·10, 90% CI 0·72 to 1·69; p<0·0001 for non-inferiority). Nevertheless, the 8% incidence of locoregional recurrence at 5 years is already substantial, presumably because of the inclusion of patients with high-risk breast cancer. Therefore, further follow-up will be

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