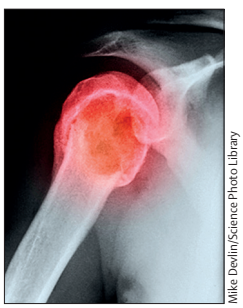
Denosumab for giant cell tumour of bone: success and limitations



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See Articles page 1719

Intralesional surgery, with or without local adjuvant, or en-bloc resection is the treatment of choice for giant-cell tumor of bone. However, recurrence rates remain high (10–50%), and surgery for tumour in common locations such as the pelvis and spine have unacceptably high morbidity. Improved targeted therapy for local and systemic control is needed. The eponymously named multinucleated giant cells are reactive and not neoplastic. The true neoplastic cells are bone forming mesenchymal stem-like cells that induce and drive the giant cells by mechanisms under study.[1] Nevertheless, new therapies have focused on disrupting the reactive giant cells and their communication with the neoplastic mesenchymal cells.

In *The Lancet Oncology*, Sant Chawla and colleagues[1] present the long-term follow-up results of their phase 2 trial of denosumab to treat giant cell tumour of bone. They expanded their trial from 282 patients in the interim analysis (published in 2013)[2] to 532 patients in the current report, and thereby have completed the largest clinical trial to date on giant-cell tumour of bone using a recently approved drug targeting receptor activator of nuclear factor-kappa β ligand (RANKL) in this rare tumour.[1,2] Their results support the main message of the Article that the drug can be used safely and with reasonable activity in both unresectable and resectable giant-cell tumours.

Overall, the treatment was beneficial to patients. The authors show that 88% of patients with unresectable disease had no progression or recurrence of disease after 60 months follow-up: a huge benefit for these patients who have few, if any, alternative treatment options. Moreover, only 28 (11%) of 262 patients with unresectable disease had on-treatment disease progression. However, in the cohort of patients with resectable disease, 42 (27%) of 157 patients who underwent surgery had disease progression. Why progression was more than twice as frequent in resectable patients than in unresectable patients remains unexplained. 31 (34%) of 90 patients with resectable disease had tumour recurrence after curettage. This outcome does not seem to be any better than previous reports with other treatments.[3,4,5] Thus, although it seems to be beneficial for unresectable tumours, denosumab should not necessarily be considered a standard therapy for resectable giant-cell tumour of bone.

As observed in clinical trials of osteoporosis and metastatic cancers to bone, denosumab had an acceptable safety profile.[1] In the 526 patients who received at least one dose of denosumab, the most common grade 3 or worse adverse effects were hypophosphataemia in 24 (5%) and osteonecrosis of the jaw in 14 (3%) patients. The large study size and long duration of follow-up enabled the authors to identify rare late complications. For example, four (1%) patients had hypercalcaemia occurring 30 days after denosumab discontinuation, and four (1%) had atypical femur fractures. Late surveillance for these complications is necessary. Overall, the adverse event outcomes are unsurprising, but reassuring findings.

The methodological limitations of this study deserve mention. Patients treated with bisphosphonates, radiotherapy, or other adjuvant treatments were excluded, which leaves the question of how the different treatments should be integrated in clinical practice unresolved. Assessment of activity was not uniformly defined and was dictated by practical considerations. For example, the authors state that there were no predefined standarised criteria for tumour assessment.[1] Retreatment periods were not included. The treating surgeon unilaterally determined that 106 (43%) of 245 patients who were eligible for on-study surgery were able to have a less morbid surgical procedure. However, the qualitative and quantitative differences in procedure morbidity were not defined.

The frequency of sarcoma development was low in the trial, but this outcome needs to be studied more thoroughly. Chawla and colleagues[1] concluded that there was sarcomatous transformation in four (1%) patients overall—a conclusion reached after the study sponsor added central adjudication of reported cases of sarcoma transformation. This post-hoc analysis excluded cases in which the patients were later found to have a pathologically confirmed misdiagnosis of benign giant cell tumour of bone.[1] In the 526 patients who received at least one dose of denosumab, 20 patients had malignancy, 15 of whom were excluded from the final analysis of

sarcomatous transformation because the investigators believed they had been misdiagnosed with giant cell tumour of bone at baseline. This unplanned adjudication eliminated three-quarters of the cancers in which the drug was either associated with sarcoma development or should never have been used. This fact is sobering. Even a small increase in the frequency of this complication alters the risk-benefit ratio of denosumab and changes the preferred treatment from drug therapy to surgery. Thorough genetic testing of tumour samples is essential to characterise these controversial cases, and ongoing post-marketing surveillance is needed to fully understand the phenomenon of sarcomatous transformation.

Worryingly high incidences of local recurrence have been reported for intralesional surgery after preoperative denosumab therapy. In difficult-to-treat cases, such as pelvic and sacral giant cell tumour, recurrence rates as high as 62% have been reported.[3] Notably, these results were from the Rizzoli Orthopedic Institute (Bologna, Italy) and the Royal National Orthopaedic Hospital (Birmingham, UK): both centres that contributed patients to the Chawla and colleagues trial.[1] These results raise questions about how effective the drug will be when used outside the structure of a clinical trial.[6]

Important questions remain unanswered regarding the disease and its treatment. What is the origin of the disease? What is its natural pathophysiology and method of control? How does the immune response modify the tumour's behaviour? What is the best way to assess response to treatment (Response Evaluation Criteria in Solid Tumours [RECIST], Choi criteria, or the Rizzoli CT system)? What is the true likelihood of local recurrence? Is there more frequent recurrence after denosumab treatment, as uncontrolled reports suggest?[6] Should the drug be used postoperatively, and for how long? What dose modification is acceptable and effective? Does combined drug therapy help, and what is the optimal method for a drug such as preliminary use of denosumab for 3 months then use bisphosphonates. Is there an increased risk of malignant transformation associated with denosumab? How should patients be monitored on long-term therapy?

Chawla and colleagues[1] show that we can now use denosumab with confidence and start to address these remaining unanswered questions. Hopefully, enough investigator, corporate, and scientific community support exists to obtain clinical answers for patients. Therapies targeting the spindle cell perpetrators of disease and not just the accompanying monocytic or giant cells might be even more effective than treatment with denosumab.

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Androgen receptor-targeted agents in the management of advanced prostate cancer

See **Articles** page 1730

Since 2010, the prostate cancer treatment landscape has been profoundly modified by the introduction of eight agents: four hormone treatments (abiraterone acetate, apalutamide, enzalutamide, and darolutamide), two chemotherapy drugs (docetaxel and cabazitaxel), the α-emitter radionuclide radium, and sipuleucel-T (a vaccine available only in the USA). These molecules were all approved within a few years of each other in parallel trials, creating a complicated conundrum: when should patients be given these drugs, in what sequence, and—most importantly—can we ascertain that their efficacy remains unchanged