Denosumab in early-stage breast cancer

We read with great interest the Article by Michael Gnant and colleagues.[1] They highlight the benefit of denosumab on disease-free survival in postmenopausal women with hormone receptor-positive breast cancer receiving aromatase inhibitor therapy. Denosumab was administered every 6 months for a median of seven doses (IQR 4–10). The median follow-up was 73 months (IQR 58–95).

The analysis and the discussion do not take into account two major concerns regarding denosumab discontinuation that could temper the conclusions: 1) the increased risk of spontaneous multiple vertebral fractures; and 2) the need to prescribe a bisphosphonate to avoid this risk.

First, in postmenopausal women with osteoporosis, denosumab discontinuation is associated with a severe rebound effect that lasts 2 years. It combines an increase in bone turnover markers and a complete loss of the gained bone density.[2] This rebound effect is associated with an increased risk of spontaneous multiple vertebral fractures,[3] occurring in at least one in every 100 patients (but fewer than one in every ten).[3] In a series including 70 women with vertebral fractures after denosumab discontinuation, a median of five (IQR 2–8) vertebral fractures occurred 7–20 months (median 11, IQR 8–16) after their last denosumab injection.[4] This adverse event concerns postmenopausal women treated for osteoporosis or for bone loss preservation in case of aromatase inhibitors therapy[3,4] and negatively affects their quality of life; therefore, it should be included in the disease-free survival analysis. Gnant and colleagues mention that adverse events were only recorded for up to 30 days after the last dose of study treatment and that adverse event data for denosumab are available from other settings, such as the FREEDOM trial.[5] A post-hoc analysis of the FREEDOM trial evaluated 1001 women 9–12 months after their last denosumab injection.[5] During this follow-up, the annualised risk of vertebral fractures was 7·1%, of which 60·7% were multiple. However, this observational study underestimates the risk due to insufficient follow-up to cover the entire duration of the rebound effect.[4,5]

Second, to limit or avoid the risk of vertebral fractures after denosumab discontinuation, the prescription of a bisphosphonate for the duration of the rebound effect is mandatory. The disease-free survival analysis should include the 3 years of denosumab treatment followed by the 2 years of bisphosphonate treatment. The benefit of denosumab could thus be reduced.

Future studies should include the full side-effects of the given treatment and the effects of the other mandatory treatments to provide a comprehensive overview of disease-free survival.

We declare no competing interests.

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