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# Predicting skeletal complications in metastatic breast cancer raises challenges

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Breast cancer is a common diagnosis and is annually responsible for the deaths of over 400,000 women worldwide [1]. Approximately, 75% of patients with metastatic breast cancer develop bone metastases [2]. Once affected by tumor, the bone may be painful and may be at risk for skeletal related events (SREs) including fracture, need for surgery or radiation to bone, or spinal cord compression. Hypercalcemia of malignancy (HCM) may also be considered an SRE, but it is often categorized as a separate adverse event. In addition, bone metastases can be associated with marrow infiltration and disruption of hematopoiesis. Not only do bone metastases implicate an incurable diagnosis, bone metastases associate with pain, decreased quality of life, and significant health care expenditure [3].

In the absence of bisphosphonate therapy, approximately, 50–60% of patients with breast cancer will develop an SRE within the 1–2 years of diagnosis of bone metastases [4-6]. SREs can occur repeatedly over the course of the disease and the risk of additional SREs increases after the first SRE [7-9].The risk of SRE likely increases as the tumor progresses in bone and further alters the bone structure. The bisphosphonates, when dosed for metastatic bone disease, have been shown to reduce the risk of SREs, including HCM, and they can reduce bone pain [10]. The bisphosphonates have been incorporated into the management of patients with metastatic breast cancer involving the bone outlined by the American Society of Clinical Oncology guidelines [11].

Using a database generated from a phase III, multicenter trial of patients with breast cancer and bone metastases, Brown et al. investigated risk factors associated with the development of SREs in 444 patients treated with zoledronic acid (4 or 8 mg) intravenously every 3–4 weeks for up to 24 months [12]. The investigators assessed 21 clinical, radiographic and biochemical variables and performed a comprehensive multivariate analysis. The diversity of variables and the multivariate analysis makes this work unique.

The results of this exploratory analysis are consistent with the literature to date, suggesting that many factors associated with disrupted bone integrity and/or bone metabolism may serve as signals for risk of SRE. The univariate analysis demonstrated the following baseline parameters significantly associated with an increased risk of on study SRE: prior history of SRE, increased age, increased number of bone lesions, predominance of osteolytic lesions, higher brief pain inventory score, higher ECOG performance status, low albumin, elevated lactate dehydrongenase (LDH), elevated urinary N-telopeptide of type I collagen (uNTX), and elevated bone alkaline phosphatase (BAP). In the multivariate model, the parameters shown statistically significant were: age (>60 years), brief pain inventory score > 3 units, prior SRE, and the predominance of osteolytic lesions. Analysis of the biochemical variables in quartiles or as dichotomized parameters affected the results and uNTX (>64 nmol/mmol), BAP ≥201.5



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U/l, and LDH ≥ upper limit of normal were shown to have statistical significance by at least one analysis technique.

The investigators went on to subtype the data into risk for fracture and risk of radiation therapy. Using either the full model analysis or the reduced model, the following factors associated with the risk for on study fracture: duration of bone metastases >12 months and prior pathologic fracture. Parameters significant only in the full model included: number of bone metastases, elevated baseline UNTX and LDH, and osteolytic lesions. Interestingly, pain was not a significant variable for risk of fracture, although it was associated with use of radiation therapy.

How might the clinician use this information to guide patient management? The bisphosphonates have already been incorporated into the care of patients with metastatic breast cancer involving the bone [10]. Will this new data impact on the initiation, dosing intervals or duration of bisphosphonate therapy? The exploratory data generated by Brown et al by itself may not change practice, but it is an important foundation to understanding risk of SREs. It is noteworthy that duration of bone metastases >12 months associated an increased risk for pathologic fracture, suggesting that initiating an osteoclast inhibitor early on in the course of disease management may be important in reducing the risk of fracture. This is consistent with data generated from a medical and pharmacy claims database by Mortimer et al. [13] which suggested that initiating an intravenous bisphosphonate within 90 days of diagnosis of bone metastases provides clinical benefit.

Addition studies will be necessary to refine SRE risk assessment and to develop an algorithm or index of SRE risk. A tool identifying patients who are more, or less likely, to benefit from bisphosphonate therapy would be clinically useful and as new bone directed therapies emerge, it will be important to assess whether all patients respond equally well to all bone modifying therapies. It is likely that in the future clinical, radiographic, pathologic, and/or genetic information will direct the use of bone modifying agents and that therapies will be more finely tailored then the present practice. As bone imaging techniques improve, upcoming clinical trials may incorporate rigorous characterization of the bone metastases and assess bone micro-architecture. In addition, future studies are likely to incorporate biomarker data, genetic as well as biochemical, to improve the ability to predict SRE risk for a particular individual.

Although there are no ongoing clinical trials with the primary endpoint of developing a tool for predicting SRE, there are a wide range of studies investing bone modifying agents in patients with metastatic bone disease that have SREs as endpoints. The data generated in these studies will add clinical and correlative study materials for continued analysis of SRE risk. If those at greatest risk for SRE can be identified, what can be done to reduce that risk beyond the standard of care for all patients with evidence of bone destruction from metastatic disease? It is difficult to calculate whether the existing tools generated by Mirels to estimate the risk of pathologic fracture [14] and the bone scan index for prognostication [15] have made an impact on patients' treatment. A future index of SRE risk would need validation for clinical utility, along with an acceptable intervention to alter that risk, prior to acceptance.

The data generated by Brown et al. clearly demonstrates that women with metastatic breast cancer involving the bone who will be treated with zoledronic acid and who have a baseline pathologic fracture are at increased risk for a future pathologic fracture and those with any baseline SRE are at risk for future SREs. At baseline, 59% of study patients had experienced a SRE, which highlights that the majority of patients are at high risk for future events. Additional studies are warranted to identify ways of reducing this risk by preventing or delaying the development of SREs and lessening all adverse events associated with bone metastases. These are important questions to address as we seek methods to prevent bone metastases all together.

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