Editorial

Cost-effectiveness in managing skeletal related events in breast cancer: a strategy of less-intense dosing schedule of bone modifying agents

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The introduction of bone-modifying agents (BMA) or skeletal protective agents in the mid 1990's into oncology armamentarium has revolutionized the management of skeletal related events (SREs) in cancer patients with established bone metastases. The health and financial burden of SREs are significantly reduced with the use of adjuvant BMAs. Several studies have presented evidence which shows that these agents help to decrease SREs, such as fractures, hypercalcemia, pain medication use, and the need for radiation and/or surgery in breast cancer patients. Additionally, their use in breast cancer patients not only decreases bone metastases but also improves the bone mineral density thus preventing osteoporotic fractures which can be associated with hormone therapy that is given to breast cancer patients.

The use of once-monthly bisphosphonates for reducing SREs in breast cancer patients was first described in American Society of Clinical Oncology (ASCO) clinical practice guidelines in 2000 (1). This notion of once-monthly dosing hailed from the experience of bisphosphonate use in patients with hypercalcemia of malignancy (2). In clinical trials, monthly administration of 4 and 8 mg doses of zoledronic acid (ZA) had comparable efficacy in reducing SREs. Additionally, the 4 mg ZA dose resulted in fewer side effects which indicate that higher doses of ZA are typically not well tolerated. It is important to note that the trials which evaluated the once-monthly 4 mg ZA were of one to 2-year duration, but it is known that cancer patients who are started on BMAs are on such agents for longer time periods (especially with the increased life expectancy of cancer patients in the modern era) (3,4). This once-monthly administration of BMAs lead to worrisome side- effects including: osteonecrosis of the jaw (ONJ), atypical femoral fractures, nephrotoxicity, hypocalcemia and other rare side effects (5). These side effects occur at a higher rate in cancer patients versus those receiving these same drugs for osteoporosis management, thereby indicating that the side-effects are dose related. BMAs were primarily approved to reduce SREs but given their benefit in disease free survival, delay in occurrence of SREs, and role in prevention of disease recurrence in post-menopausal breast cancer patients (also in other solid malignancies such as prostate cancer), BMAs are being administered in all the patients who have skeletal metastasis irrespective of disease burden. The patients with less disease burden may not need this frequent dosing compared to those with a higher disease burden. Additionally, pharmacodynamic data of bisphosphonates shows that they are well-incorporated in bone tissue and have activity in bone for approximately 10 years (6). This finding has led researchers to analyze the concept of less frequent dosing of bisphosphonates in reducing SREs in cancer patients.

Recent randomized trials have shown that ZA every 3 months was non-inferior to monthly ZA in reducing SREs in patients with breast cancer (7,8), prostate cancer and multiple myeloma with skeletal metastases (9). Though

these trials have had some limitations, they have shown consistent results in establishing the non-inferiority of 3-month dosing of ZA (10).

Globally the financial burden of cancer therapy is an ongoing challenge and is not unique to one drug company or one product. It is well-known that cost-effective cancer care is directly related to drug costs rather than initial diagnostic testing. Health care cost-benefit analysis provides data to assist physicians in determining the optimal treatment strategies for cancer patients. The patient and physician surveys show that both the patients and oncologists are willing and looking forward for de-escalating dosing regimens (4,11). This extended inter-dose time interval of 3 months is a potential solution to the substantially increasing costs of cancer treatment in appropriately selected subset of patients, and this 3-monthly dosing regimen has the potential to expand affordability in patients.

This has prompted the development of therapeutic strategies considering the risks/benefits, impact on quality of life, and costs of specific drug therapies. Shapiro *et al*., have used such an approach to ascertain cost-effective strategy in preventing skeletal complications in breast cancer patients (12). Their findings have implications on the application of cost-effective strategy in already expensive cancer care that may serve as a precedent to do the same with other drug regimens. Shapiro and colleagues performed a cost-effectiveness analysis comparing every 3 months of ZA versus monthly denosumab in a retrospective observational study using Markov probability model (12). The study analyzed the cost-analyses between the two drugs by assuming various probabilities of SREs-higher, lower and equal probability in ZA group compared to that of denosumab group. Though monthly denosumab is efficacious in reducing SREs in terms of cost-effectiveness, the 3-monthly ZA group was superior than denosumab. Per the study analysis, the monthly denosumab is 9-fold more expensive than generic every 3-month ZA. Though the study carries the limitation of Markov model, the authors should be commended for considering all potential probabilities of higher and lower SRE rates in either of the drugs analyzed. The other noteworthy point in the study is that it was performed without any pharmaceutical company support. Previous studies that analyzed the cost-effectiveness of ZA and denosumab were supported by their respective pharmaceutical companies (13-16). In these studies, ZA was proven to be effective in the study that was supported by the makers of ZA and denosumab was proven to be effective in the study that was supported by denosumab makers. The study by Shapiro and colleagues does not have this "pharmaceutical company support bias".

One must be cautious though when interpreting the study results. This study did not take into consideration the location of bone metastasis and treatment regimen that the patient is on. For example, if the patient has high disease burden in the axial skeleton (e.g., spine) and is on GnRH agonist therapy, his/her risk of SREs and related comorbidity is very high compared to a patient who has a low skeletal disease burden or who has only appendicular skeletal metastasis. In such patients who are at increased risk of having an SRE, physicians and patients may tend to prefer the most efficacious agent (in this case, denosumab, which prevents SREs 23% more than that of ZA) to prevent any SREs (17).

Another point to consider is that though the study concluded that the costs associated with denosumab in preventing 1 SRE ranged up to $347,655 (USD), it did not comment on the hospitalization costs and other associated comorbidities in an event of SRE. For example, in an event of spinal cord compression, the estimated cost of management mentioned in the study was around $67,000 (USD). In practical scenario, the actual cost to manage a SRE may in fact be much higher and depends on multiple confounding variables such as: length of hospital stays, level of care (intensive care unit versus general medical floor), associated comorbidities, medications (the cost of medications received in-hospital setting is much higher than out-patient setting), nursing care costs and other miscellaneous costs.

The question that arises is whether 3-monthly ZA can replace monthly denosumab or ZA as the new standard for adjuvant therapy in prevention of SREs in breast cancer patients on hormonal and chemotherapy regimens? As discussed above, the three randomized trials have shown that 3-monthly dosing of ZA represent an acceptable treatment alternative (7-9). The benefits of this extended inter-dosing interval are linked to fewer patients experience with side effects of ZA (ONJ and nephrotoxicity) and most importantly without compromising the efficacy of the drug. Moreover, results from Shapiro *et al*., study imply that there is a definite cost-effective advantage especially in the current medical healthcare systems where affording health care has become a pressing global concern. However, this data should be interpreted with caution given that the follow up in these non-inferiority trials is for 2-year and no long-term

data beyond the 2-year time frame is currently available. It is also important to note that the data are mainly derived from breast cancer patients and may not be directly be extrapolated to other cancers.

Finally, when comparing the two drugs: ZA versus denosumab resulted in fewer SREs compared to ZA, which might be preferred in patients, irrespective of the cost), at very high risk of having SREs (17). The final decision of whether to administer 3-monthly ZA or monthly denosumab should be made during the consultation between the patient and his/her oncologist. The following factors must be taken into consideration: medical comorbidities, financial matters, disease burden, type of hormonal therapy (bone loss with GnRH agonists is higher compared to other hormonal therapies, thus having a potential for higher SREs) and weighing benefits and risks assessment. Also, the patient preferences should be considered while choosing an appropriate therapy. Nevertheless, recent trails show that 3-monthly administration of ZA is equally effective in reducing SREs and assisting with a lower financial burden on the patient and their family.

In conclusion, the findings from Shapiro *et al*. study have practical implications for the application of cost-effective strategy in an already expensive cancer care and may serve as a precedent to consider the same with other drug regimens. In a very rare occasion, a single study (e.g., this study by Shapiro *et al*.,) can completely change the way medicine is practiced but the accumulating evidence from multiple studies can help clinicians make an educated evidence based clinical judgement in formulating new guidelines. There is a pressing need (especially in the field of oncology where drugs involved in cancer care are very expensive) for non-pharmaceutical company funded and non-biased studies to deliver the most cost effective and highest quality care to our patients with the goal to provide the same level of care that we wish for our family members or ourselves.

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Footnote

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