SYSTEMATIC REVIEW OF SKELETAL-RELATED EVENTS IN BREAST CANCER

Broder MS,[1] Gutierrez B,[2] Linhares Y,[1] Cherepanov D[1]
[1]Partnership for Health Analytic Research, LLC, [2]Bristol-Myers Squibb, Lawrenceville, NJ, USA

Objectives

Metastatic bone lesions lead to an increase in the risk for skeletal-related events (SREs), including pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and severe bone pain requiring palliative radiotherapy or surgery to bone. Twenty-nine percent of breast cancer patients with bone metastases develop SREs (Colleoni et al. 2000; Coleman et al. 1987).

Our objective was to systematically review the literature on the impact of SREs on pain, quality of life (QOL), morbidity, survival, and cost in patients with metastatic bone disease from multiple myeloma or from cancers of the prostate, breast, lung, and kidney. In this review, we describe our findings from the systematic literature review of patients with breast cancer.

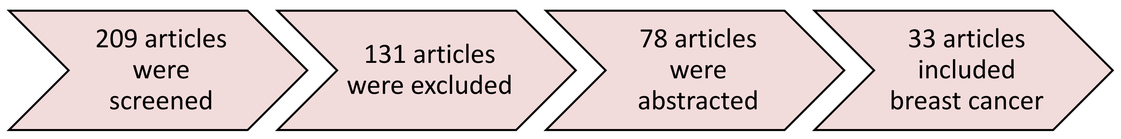
Methods

We searched PubMed for peer-reviewed English-language human studies published in 2000-2010. The search was based on a definition of an SRE accepted by the U.S. Food and Drug Administration and the European Medicines Agency (EMA). Search strategy key terms included “fracture,” ”spinal cord compression,” “hypercalcemia,” “skeletal related events,” “metastatic bone cancer,” “radiation therapy,” “bone surgery,” “skeletal surgery,” “spine surgery,” and “bone pain” for cancers of interest.

Articles were included if they were randomized controlled trials, clinical trials with an appropriate control group, systematic reviews, meta-analyses, case series, or economic analyses; articles were excluded if they did not provide interpretable results on outcomes of interest. Articles on denosumab were not included in this review since they were published after our systematic search was completed.

Results

- A total of 209 articles were screened, of which 131 were excluded and 78 were abstracted.
- Thirty-three of the 78 abstracted articles included breast cancer patients.



Overview of Systematic Literature Review Results in Breast Cancer

We did not identify any studies, outside of bisphosphonate trials, that examined the impact of SREs as a group on clinical outcomes.

- Bisphosphonate treatment reduced SREs, and hence decreased pain and improved QOL (see table 1).
- Studies in the literature indicated that the presence of pathologic bone fractures is associated with increased risk of death (see table 2).
- Spinal cord compression significantly impaired ambulatory function and shortened survival of breast cancer patients compared with historical controls (see table 2).
- Radiation therapy decreased pain and improved QOL, whereas bone surgery was shown to decrease pain and improve function with vertebrectomy (see table 3).
- Two studies suggested treatment cost of SREs:
  - $14,000 USD (95% CI: $11,000-$17,000) per patient for SREs as a group (Delea 2006)
  - £18,000 (GBP), about $28,500 USD, for a proximal femoral replacement surgery (Ashford 2010).

Table 1. Impact of Skeletal-Related Events as a Group

	Pain	Quality of Life	Morbidity	Survival
SREs as a Group	Decreased in patients treated with bisphosphonates, which reduce SREs (Body 2004; Carteni 2006; Diel 2004; Pavlakis 2005; Tripathy 2004).	Lower QOL in patients with SREs and improved in patients treated with bisphosphonates, which reduce SREs (Body 2004; Carteni 2006; Diel 2004; Pavlakis 2005; Weinfurt 2004).	Skeletal morbidity reduced with bisphosphonates (Tripathy 2004) but no change on ECOG PS (Carteni 2006).	No reports of benefit with bisphosphonates (Diel 2004; Pavlakis 2005).

Note: Eastern Cooperative Oncology Group performance status (ECOG PS).

Table 2. Clinical Skeletal-Related Events

	Morbidity	Survival
Malignant Bone Fracture	No data	• Saad et al. (2007) indicated that patients who developed fractures had a 19%-52% increased risk of death compared with patients who had no fractures (P<.01).
Spinal Cord Compression	• Rades et al. (2006) reported that of the 23% patients who were nonambulatory before radiation therapy for spinal cord compression, 39% regained the ability to walk posttherapy.	• In the study by Rades et al. (2006), median survival was 20 months (23% died within 6 months and 36% within 12 months posttherapy). • van der Linden et al. (2005) reported that after a diagnosis of spinal cord compression, median overall survival was 1 month (mean overall survival: 4 months; 95% CI: 2 weeks - 8 months).

Note: No studies were found on the impact of bone fractures or spinal cord compression on pain or QOL;
No studies were found on the impact of hypercalcemia on any outcome of interest.

Table 3. Impact of Treatment (Radiation Therapy, Bone Surgery) of Clinical Skeletal-Related Events

	Pain	Quality of Life	Morbidity	Survival
Radiation Therapy	• 20%-45% patients achieved complete pain relief and reduced scores on the visual analogue scale (VAS) (Hamouda 2007; Hartsell 2005; Hird 2009; Kouloulias 2003; Salazar 2001; Sze 2004).	• Salazar et al. (2001) used net pain relief as a measure of QOL to report that on average patients lived 70% of their remaining lifetime pain-free. • Kouloulias et al. (2003) found that QOL scales improved posttherapy.	• Hartsell et al. (2005) recorded incidence of fractures in 2 treatment arms (5%, 8%). • Kouloulias et al. (2003) reported that the median time from baseline without any skeletal morbidity was 17 months.	• Djabelek-Maciaś et al. (2006): 85%-100% of patients alive at 20-month and 0-50% at 125-month follow-up. • Median survival of 14.1-23.5 months posttherapy (Kouloulias 2003; van der Linden 2005). • Patients with complete pain relief had better survival than patients who responded partially (van der Linden 2005; Salazar 2001).
Bone Surgery	• VAS scores decreased postsurgery: 50% at VAS=0 (Gerszten 2005; Liberman 2009). • 67% of patients had a reduction in opioid use (Liberman 2009). • Improved pain control: 71%-75% (Ibrahim 2008; Deutsch 2008).	No data	• Deutsch et al. (2008): in 2 of 3 treated patients, one regained ability to walk whereas the second achieved normal function.	• Deutsch et al. (2008) reported that 33% of patients with a baseline 1-year life expectancy were alive at 1 year postsurgery. • Median survival was 11.7 months (95% CI: 291-421 days), with a 52% 1-year and 35% 2-year survival (Ibrahim 2008).

Additional Considerations

- Although radionuclide therapy (RNT) is not part of the FDA- or EMA-accepted definition of SREs, studies of RNT were identified under the topic “radiation therapy” in our systematic search.
- Out of 20 identified RNT studies, 7 studies reported that RNT for SREs decreased pain and morbidity in breast cancer patients:

Table 4. Impact of Radionuclide Therapy

	Pain	Quality of Life	Morbidity	Survival
Radionuclide Therapy	Decreases pain in 37%-80% of patients (Liepe 2005, 2007; Nilsson 2005; Dolezal 2009; Tripathi 2006; Bączyk 2007; Yaneva 2005).	No data	Decreased on the Karnofsky performance scale (Liepe et al. 2005b; Bączyk et al. 2007).	No data

Conclusions

- In summary, the presence of clinical SREs among breast cancer patients is associated with worse morbidity and survival, whereas treatment of SREs is associated with decreased pain, improved QOL, and decreased morbidity.
- In addition, the presence of SREs appear to substantially increase the cost of treatment.
- Our literature review indicates that treatment of breast cancer metastatic to bone that reduces SREs will improve clinical outcomes and reduce the cost-related burden of the disease.

References

Ashford et al. *Int Orthop.* 2010;34:709-713.
Bączyk et al. *Nucl Med Commun*. 2007;28:245-250.
Body et al. *Pain.* 2004b;111:306-312.
Cartenì et al. *Oncologist.* 2006;11:841-848.
Coleman RE, Rubens RD. *Br J Cancer*. 1987;55:61-66.
Colleoni et al. *J Clin Oncol*. 2000;18:3925-3935.
Delea et al. *J Support Oncol.* 2006a;4:341-347.
Deutsch et al. *J Spinal Disord Tech.* 2008;21:101-105.
Diel et al. *Eur J Cancer*. 2004;40:1704-1712.
Djabełek-Maciaś et al. *Nucl Med Rev Cent East Eur.* 2006;9:138-143.
Dolezal J. *Onkologie.* 2009;32:35-39.
Gerszten et al. *J Neurosurg Spine*. 2005;3:296-301.
Hamouda et al. *Gulf J Oncolog*. 2007;1:35-41.
Hartsell et al. *J Natl Cancer Inst.* 2005;97:798-804.
Hird et al. *Int J Radiat Oncol Biol Phys*. 2009;75:193-197.
Ibrahim et al. *J Neurosurg Spine*. 2008;8:271-278.
Kouloulias et al. *Int J Radiat Oncol Biol Phys.* 2003;57:143-157.
Liberman et al. *Ann Surg Oncol*. 2009;16:140-146.
Liepe et al. *J Cancer Res Clin Oncol.* 2005a;131:60-66.
Liepe et al. *Am J Hosp Palliat Care*. 2005b;22:457-464.
Liepe et al. *Nucl Med Commun.* 2007;28:623-630.
Nilsson et al. *Clin Cancer Res.* 2005a;11:4451-4459.
Pavlakis et al. *Cochrane Database Syst Rev.* 2005;3:1-45.
Rades et al. *Int J Radiat Oncol Biol Phys*. 2006c;64:182-188.
Saad et al. *Cancer*. 2007;110:1860-1867.
Salazar et al. *Int J Radiat Oncol Biol Phys*. 2001;50:765-755.
Sze et al. *Cochrane Database Syst Rev.* 2004;2:1-32.
Tripathi et al. *Indian J Cancer*. 2006;43:86-92.
Tripathy et al. *Ann Oncol*. 2004;15:743-750.
van der Linden et al. *Cancer*. 2005;103:320-328.
Vogel et al. Oncologist. 2004;9:687-695.
Weinfurt et al. *Med Care*. 2004;42:164-175.
Yaneva et al. *Folia Med(Plovdiv)*. 2005;47:63-69.

Supported by funding from Bristol-Myers Squibb Company