Modern Multidisciplinary Care in Spine Tumors

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Trends in Cancer Mortality

The American Cancer Society estimates just over 1.6 million new cancer diagnoses in 2019, compared to over 1.7 million in 2018 [1, 2]. As incidence declines, cancer-specific mortality improves. The annual decrease in cancer death rate in men and women is 1.8% and 1.4%, respectively. Importantly, the cancer death rate has dropped by 27% from 1991 to 2016 translating to over 2.6 million fewer cancer deaths than would have occurred had cancer incidence remained at its peak [1].

The improvement in cancer incidence and mortality is multifactorial. Significant efforts have been made toward early detection. One such effort was the National Lung Screening Trial (NLST), a randomized study comparing annual low-dose chest computed tomography (CT) to chest radiograph as a screening modality in high-risk individuals, which showed a significant relative risk reduction in mortality in lung cancer with early detection [3]. Reduction in tobacco use is also related to decreased cancer incidence, with the Centers for Disease Control and Prevention (CDC) report a decline in current smokers from 20.9% in 2005 to 14% in 2017, with an associated increase in even smokers who have quit [4]. Finally, advances in systemic therapy for local and metastatic disease have largely contributed to decreased cancer mortality. These include widespread use of targeted therapies such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, and immunotherapy such as checkpoint inhibitors. It is, therefore, increasingly important to recognize these trends to allow appropriate multidisciplinary decision-making when approaching patients with advanced disease, specifically those with spine involvement which can be associated with a significant burden of cancer morbidity for these patients.

Lung adenocarcinoma is a notable example where multidisciplinary care has led to dramatic improvements in survival. Overall prognosis for lung adenocarcinoma has traditionally been poor, particularly in the metastatic setting in which the 5-year overall survival is less than 10% [5]. However, a subset of patients with advanced non-small-cell lung cancer (NSCLC) harbor activating mutations in epidermal growth factor receptor (EGFR), the receptor tyrosine kinase ROS1, or anaplastic lymphoma kinase (ALK) for which targeted therapies are now available. Recently, the third-generation EGFR-TKI osimertinib was found to be associated with a progression-free survival (PFS) of 18.9 months compared to 10.5 months with first- or second-generation TKI [6]. This benefit was also noted in patients with brain metastases, in which the median PFS of central nervous system (CNS) disease was

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15.2 months for osimertinib compared to 9.6 months with first- or second-generation TKI. Several additional studies of various TKIs including alectinib, ceritinib, and crizotinib have shown improved PFS, many of which had durable responses [7–9]. Spinal metastases remain a major source of morbidity in patients with advanced lung cancer, with over 50% of advanced lung cancer patients with bone metastases found to have spinal involvement. Novel systemic agents may allow for a more aggressive approach to spinal metastases that historically were considered futile. In fact, the presence of activating mutations in patients with spinal metastases was associated with an improved overall survival (HR 0.38, $p = 0.03$) [10]. Thus, nuances in diagnosis and treatment must be weighed when intervention is being considered.

Over the past decade, our understanding of the immune system's role in cancer has evolved, and the use of immunotherapy has contributed to improved survival in several solid tumors. In randomized studies, checkpoint inhibition with anti-PD1/PDL1 antibodies alone or in combination with cytotoxic chemotherapy have consistently shown significant improvement in overall survival in the metastatic setting compared to chemotherapy alone [11, 12]. One-year survival in metastatic melanoma has improved from approximately 25% in the pre-immunotherapy era to a 3-year OS rate of 63% with dual checkpoint blockade [13]. Checkpoint inhibitors alone or in combination with tyrosine kinase inhibitors have also significantly improved PFS and OS in metastatic renal cell carcinoma [14, 15].

Each of the diseases discussed above have a propensity to develop spine metastases, leading to significant morbidity and mortality for patients. Historically, aggressive local therapies were avoided due to the overall poor prognosis of this patient population. However, it is imperative to consider the improved survival in the era of novel systemic therapies when determining whether aggressive intervention in the setting of spinal metastases should be undertaken. A multidisciplinary approach can offer opportunities for meaningful treatment options and prognosis improvements.

Systemic Therapy for Primary Bone Tumors

Primary bone tumors involving the spine may be benign, such as giant cell tumor of bone (GCTB) or malignant, including osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma. Management of osteosarcoma and Ewing sarcoma with multi-agent chemotherapy, possibly in combination with surgery and/or radiation therapy, remains the standard of care. Historical clinical trials, primarily in the pediatric population, have clearly demonstrated the role for surgery and/or radiation interdigitated with chemotherapy [16, 17]. Attempts to improve outcomes by intensification of chemotherapy based on percent viable tumor on resected specimen in osteosarcoma were unsuccessful resulting in little change to the treatment paradigm of these tumors [18]. While there have been few advances, the standard approach to management of these tumors continues to require close multidisciplinary collaboration.

Chondrosarcoma, the second most common primary bone tumor after osteosarcoma, most commonly occurs in the pelvis [19, 20]. Surgery has remained the mainstay of treatment because of the tumor's relative insensitivity to chemotherapy and radiation. However, given the tumor's propensity for axial locations, surgical resection can be challenging. Furthermore, the utility of surgical intervention is reduced in the metastatic setting prompting the need for development of more effective systemic treatment options. Mutations in IDH1/2 lead to hypermethylation of DNA and histones resulting in enhanced tumorigenesis [21]. Importantly, more than 50% of conventional chondrosarcomas harbor somatic mutations of IDH, making this an attractive therapeutic target [22, 23]. Ongoing clinical trials are evaluating the role of IDH inhibitors in various solid tumors including chondrosarcoma (NCT02073994, NCT02273739, and NCT02481154). Additional pathways that may serve as therapeutic targets in chondrosarcoma include the hedgehog pathway, SRC pathway, and mTOR pathway. Results of these investigations are promising and if proven efficacious may

significantly alter the treatment paradigm and long-term prognosis for chondrosarcoma including opportunities for combined modality approaches.

Chordoma, a malignancy of the notochord remnants, is a primary malignancy of the axial skeleton for which en bloc resection remains standard of care [24]. However, given the location of these tumors, complete resection is often not feasible. Radiation therapy has been known to provide both a therapeutic and palliative advantage when complete surgical resection is not recommended [25–27]. Systemic therapy options for chordoma are limited, with cytotoxic chemotherapy having little efficacy [28]. A phase II study of the multi-kinase inhibitor imatinib in advanced chordoma showed a clinical benefit rate of 64% with duration of 6 months or longer [29]. Additional studies have evaluated the role of other TKIs in advanced chordoma including sunitinib and sorafenib, though these agents have never been compared head-to-head [30, 31]. A subset of chordomas exhibit EGFR mutations, and in these cases lapatinib, an oral EGFR inhibitor, has shown activity [32]. Brachyury, a transcription factor involved in notochord development, has been known to be overexpressed in chordoma [33]. There are ongoing clinical trials evaluating therapeutic strategies that exploit this overexpression, specifically drug therapy in combination with radiation (NCT03595228, NCT02383498).

Giant cell tumor of bone (GCTB) is a rare, benign but locally aggressive skeletal tumor that typically occurs after skeletal maturity in patients in their 20s and 30s [34]. In the United States, GCTB represents 15–20% of all benign bone tumors [34]. GCTB, though generally benign, does represent a spectrum of neoplasia and has unpredictable clinical behavior. Malignant transformation is rare, but in a Swedish population-based registry, malignancy accounted for up to 8% of all diagnoses of GCTB [35]. While complete surgical resection may provide the most durable local control, alternative treatment strategies may provide good disease control with functional advantages, such as joint preservation. GCTB often occurs in the appendicular skeleton, but spinal GCTB are not infrequent and pose a treatment challenge. Spinal tumors are considered to have an overall worse prognosis compared to appendicular tumors with a higher rate of local recurrence, likely due to difficulty in achieving a negative margin resection [36, 37].

Bone remodeling is modulated by production of receptor activator of nuclear factor κB ligand (RANKL) by osteoblasts. Osteoclasts are dependent on RANKL, and in its absence undergo apoptosis. GCTB have high expression of RANKL on neoplastic stromal cells resulting in activation of RANK-positive osteoclast-like giant cells [38, 39]. Denosumab, a human monoclonal antibody against RANKL, blocks interaction between the tumor stromal and osteoclast-like giant cells resulting in loss of both cell types and reversal of osteolysis. Based on its mechanism of action, denosumab was evaluated in patients with locally advanced or recurrent GCTB and shown to halt bone destruction and induce tumor regression in 20/20 patients when administered subcutaneously at a dose of 120 mg every 4 weeks [40]. An international phase II study of denosumab in GCTB is ongoing with interim analysis showing tumor response in 163/169 patients after a median follow-up of 13 months [41]. Patients enrolled in this trial have received denosumab monthly for a minimum of 6 years with some of the patients receiving drug for more than 8 years. Therefore, neoadjuvant denosumab may be used to reconstitute the bony shell and aid in complete surgical resection. Figure 5.1 shows representative MR images for a patient with a spinal/paraspinal GCTB pre-denosumab (A-C) and after 3 months of treatment (D-E). The patient subsequently underwent complete resection. For patients who are deemed inoperable, denosumab offers a reasonable treatment option for control of disease and improvement in symptoms. However, as therapy is administered monthly, treatment-related toxicities including osteonecrosis of the jaw (ONJ) and atypical bone fracture are observed in higher frequency than in patients receiving therapy for osteoporosis. It was recently reported that 6% of patients on long-term denosumab for GCTB developed ONJ while 4% developed atypical bone fracture [42]. This is compared to 1%

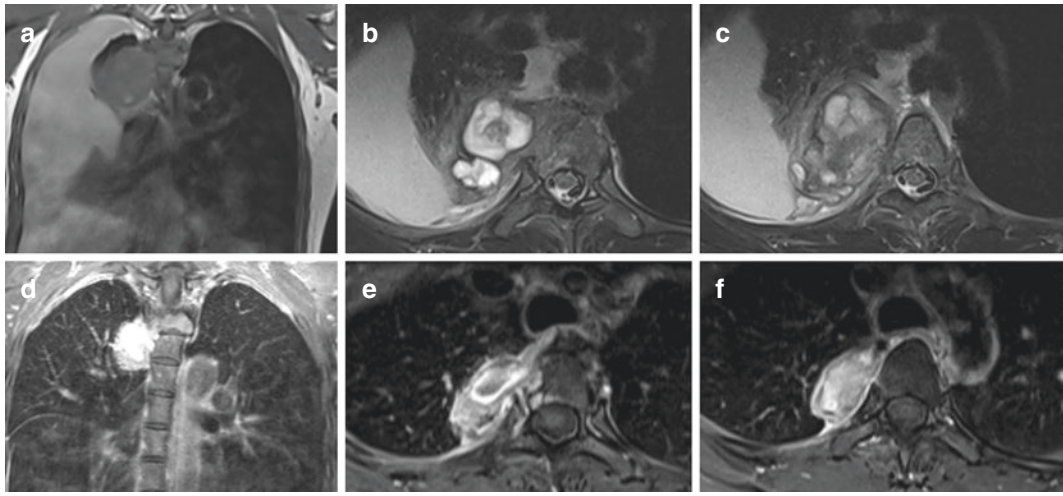

Fig. 5.1 Spinal/paraspinal GCTB before (**a**–**c**) and after (**d**–**f**) 3 months of denosumab. Coronal T1 (**a**); axial T2 (**b**, **c**); T1 gadolinium with fat saturation; coronal (**d**); and axial (**e**, **f**)

incidence in patients receiving therapy for osteoporosis. Thus, close monitoring for toxicity is important when receiving therapy long-term.

Systemic Therapy for Metastatic Disease

Bone metastases are unfortunately increasingly common, particularly in patients with advanced lung, prostate, renal, thyroid, and breast cancer. As both systemic and local treatment modalities continue to improve, the approach to patients with metastatic disease to bone is no longer limited to single modality therapy. Several approaches with combined systemic and local therapy to augment response have provided encouraging results. For example, TKI and immunotherapy have both been shown to enhance tumor response to radiotherapy. Renal cell carcinoma (RCC) is traditionally felt to be relatively radioresistant, with higher doses of radiation needed to achieve response [43]. Multiple TKIs have shown efficacy in metastatic RCC. Interestingly, a retrospective analysis in RCC patients receiving stereotactic radiosurgery for metastatic RCC to the spine noted significantly improved local control rate in patients receiving concurrent front-line TKI therapy [44]. Synergy with combination immunotherapy and radiation therapy has also been reported. Radiation can induce antigen expression, release pro-inflammatory cytokines that recruit immune cells, promote antigen cross-presentation, and induce tumor expression of death receptors [45, 46]. Therefore, combining radiation with immunotherapy may have synergistic effects and is being explored in multiple cancers including lung and others. While this may be an attractive approach to management of local disease, this treatment strategy may also apply to the metastatic setting, particularly in the situation of oligometastatic disease where resection may not be feasible. These are just a few examples that highlight how a multidisciplinary approach may greatly improve long-term outcomes for patients with advanced disease.

While treatment of existing bone metastases often provides palliation to patients, it is important to consider options for prevention of further bone metastases. Bisphosphonates such as zolendronic acid and RANKL inhibitors such as denosumab have been evaluated in this setting in multiple diseases at risk for bone involvement including multiple myeloma, breast cancer, and prostate cancer. Direct comparison of denosumab vs. zolendronic acid in patients with multiple myeloma and bone disease showed that monthly denosumab was noninferior to monthly

zolendronic acid for time to first skeletal-related event (HR 0.98, 95% CI 0.85–1.14) [47]. However, in men with castration-resistant prostate cancer, denosumab was superior to zolendronic acid in prevention of skeletal-related events (HR 0.82, 95% CI 0.71–0.95, $p = 0.0002$) [48]. Denosumab was also found to be superior to bisphosphonates in breast cancer patients with bone metastases for reducing skeletal-related events (RR 0.78, 95% CI 0.72–0.85, $p < 0.00001$) [49]. Interestingly, combination of zolendronic acid with hypofractionated radiation therapy for treatment of vertebral metastases in various solid tumors was well tolerated and suggested a reduction in the rate of vertebral collapse with improved pain and adequate tumor control [50]. Together these data inform on the use of preventative agents, as well as potential for combination with radiation to improve disease control and patient symptoms.

Perioperative Drug Safety

As previously highlighted, the efficacy of systemic therapies continues to improve, resulting in improved overall survival even in advanced disease. Therefore, there is a trend toward a more aggressive approach in the management of metastatic disease including utilization of radiation, surgery, vertebral augmentation, and ablative procedures. In patients receiving novel therapies including TKI, immunotherapy, etc., it is important to consider the implications of treatment on bleeding risk and wound healing when surgical interventions are planned as these risks differ from traditional cytotoxic chemotherapy.

Agents that have antiangiogenic activity including bevacizumab or TKI with VEGF inhibition can lead to impaired wound healing and increased bleeding. Several studies have evaluated perioperative complications with the use of these agents to identify the optimal time between treatment and surgical intervention. Withholding systemic treatment in the metastatic setting has implications on overall tumor burden, thus one must be thoughtful about the risks and benefits of the duration of any periprocedural drug holding period.

Bevacizumab has a half-life of 20 days, thus the general consensus is to hold for at least 4 weeks prior to surgery. Oral TKIs with VEGF inhibition have a much shorter half-life and can be held for a shorter period of time in the perioperative setting. Studies in renal cell carcinoma suggest a 3 day washout for sorafenib, 1 week for sunitinib, and 5–7 weeks for bevacizumab [51, 52]. Another case series of TKI and surgery in RCC suggested a washout of 2 weeks [53].

While there are no widely agreed upon guidelines, Table 5.1 outlines general recommendations for holding drugs perioperatively to ensure adequate wound healing and minimize risk of bleeding complications. Of importance, each TKI has its own labeling instructions for the recommended duration for which the drug should be held before and after invasive procedures. It is imperative to discuss timing of surgery with the medical oncologist to determine when the patient should be instructed to hold the drug with attention being given to each patient's individual risk factors in the context of systemic therapy.

There is no clear consensus on the perioperative management of immunotherapy. A single-institution, retrospective analysis showed immune checkpoint inhibitors to be safe in the perioperative setting in multiple diseases and

Table 5.1 Guidelines for perioperative management of systemic therapies

Drug category	Preoperative hold	Postoperative hold
Antiangiogenic agents (pazopanib, sunitinib, bevacizumab, axitinib)	Bevacizumab[a]: 4–6 weeks Other: 1–2 weeks	Bevacizumab[a]: 4 weeks Other: 1–2 weeks
TKI without angiogenesis effect (imatinib)	No hold	Resume when tolerating oral intake
Immunotherapy	No hold	No hold
Cytotoxic chemotherapy	3–4 weeks based on individual patient count recovery	2–4 weeks based on wound healing progress and surgeon clearance

[a]Longer perioperative hold recommended for bevacizumab due to 20-day half-life

various surgical procedures [54]. In that series, the median time from last dose to surgery was 16 days (1–32 days), and the median time from surgery to first dose was 18 days (8–14 days). The wide range exhibited even within a single institution highlights the lack of consensus. As immunotherapy is being evaluated in the neo-adjuvant setting, available data regarding safety of these agents in the perioperative setting allow for more informed recommendations. Of interest, immunotherapy has been proposed as a possible intervention to reduce postoperative immuno-suppression and thus reduce perioperative tumor growth, supporting the safety of these agents in the perioperative period [55]. Therefore, gaps in therapy are not likely required.

It is important to understand and recognize that patients receiving immunotherapy are at risk of hypophysitis and adrenal insufficiency. The rate of these drug-related toxicities varies by agent and is reported at an incidence rate of <0.1 to 6.4% [56]. Patients may be on long-term hormone replacement including levothyroxine and hydrocortisone. If not appropriately recognized, these patients could suffer adrenal crisis in the postoperative setting.

Conclusion

As systemic therapies improve, overall survival for patients with primary or metastatic spinal tumors also continues to improve. This must be considered in development of treatment plans in the metastatic setting as combined modality approaches should be considered. A multidisciplinary approach is essential to ensure opportunities for meaningful intervention are not missed. Furthermore, close communication between the surgeon and the medical oncologist is imperative to ensure appropriate management of systemic therapies in the perioperative setting.

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