Benign Tumors of the Spine

Has New Chemotherapy and Interventional Radiology Changed the Treatment Paradigm?

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Study Design. Clinically based systematic review.
Objective. To determine the role of (A) medical treatment and (B) interventional radiology as either adjuvant or stand-alone treatment in primary benign bone tumors of the spine.
Methods. A multidisciplinary panel of spine surgeons, radiation oncologists, and medical oncologists elaborated specific focused questions regarding aneurysmal bone cyst, giant cell tumor, and osteoid osteoma. Denosumab, bisphosphonate, interferon, bone marrow aspirate, doxycycline, thermal ablation, and selective arterial embolization were identified as areas of interest for the article. A systematic review was performed through MEDLINE and EMBASE. Recommendations based on the literature review and clinical expertise were issued using the GRADE system.
Results. The overall quality of the literature is very low with few multicenter prospective studies. For giant cell tumor, combination with Denosumab identified 14 pertinent articles with four multicenter prospective studies. Nine studies were found on bisphosphonates and six for selective arterial embolization. The search on aneurysmal bone cyst and selective arterial embolization revealed 12 articles. Combination with Denosumab, Doxycycline, and bone marrow aspirate identified four, two, and three relevant articles respectively. Eleven focused articles were selected on the role of thermal ablation in osteoid osteoma.
Conclusion. Alternative and adjuvant therapy for primary benign bone tumors have emerged. Their ability to complement or replace surgery is now being scrutinized and they may impact significantly the algorithm of treatment of these tumors. Most of the data are still emerging and further research is desirable. Close collaboration between the different specialists managing these pathologies is crucial.
Key words: aneurysmal bone cyst, bisphosphonate, bone marrow aspirate, denosumab, doxycycline, giant cell tumor, interferon, osteoid osteoma, selective arterial embolization, thermal ablation.
Level of Evidence: N/A
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Giant cell tumor of the bone (GCT), aneurysmal bone cyst (ABC), and osteoid osteoma (OO) are benign active/aggressive tumors. Surgery has been the mainstay of the treatment with either intralesional or en bloc resection. Surgical treatment of primary bone tumors is associated with significant morbidity and mortality.1–3 Alternative therapies and adjuvant treatments have been developed with the goal of reducing morbidity while achieving similar, if not better, outcomes. In recent years, there has been growing interest in the use of Denosumab, interferon, and bisphosphonate as an adjuvant in the treatment of GCT. Case series where selective arterial embolization (SAE) has been used as a stand-alone treatment of ABC have been published. Thermal ablation of osteoid osteoma is accepted as a standard of care in the appendicular skeleton and is now making its way to the spinal axis. The exact role, safety, and effectiveness of these alternative/adjuvant treatments remain to be defined.

A systematic review designed to answer two clinically relevant research questions was developed through consensus among a multidisciplinary panel of experts:

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What is the role of medical treatment as a preoperative adjuvant option and definitive treatment of GCT and ABC?

What is the role of interventional radiology as an adjuvant option and treatment of GCT, ABC, and OO?

MATERIALS AND METHODS
A thorough systematic review was carried on the alternative and adjuvant treatments for primary benign bone tumor. The AOSpine Knowledge Forum Tumor (AOSKFT), a panel of experts consisting of spinal surgeons, medical and radiation oncologists dedicated to treating spinal tumors, subsequently designed specific focus questions/keywords reflecting the emerging treatments. For GCT, the roles of Denosumab, interferon, bisphosphonate, and selective arterial embolization were areas of interest. For ABC, research would be conducted on selective arterial embolization, doxycycline, Denosumab, and autologous bone marrow aspirate. The role of thermal ablation in OO was also selected. Thermal ablation refers to radiofrequency ablation or laser photoagulation.

An electronic database search of the English language articles from MEDLINE and EMBASE from 1950 to February 7, 2016 was performed. Each abstract was individually reviewed to identify pertinent articles that were subsequently obtained. Reference lists from relevant articles were searched for additional articles.

Using the GRADE methodology, the quality of the evidence found in the literature was assessed. Specific recommendations by the multidisciplinary panel were issued. These recommendations are based on the combination of clinical expertise balancing risk/benefit ratio and evidence. The strength of the recommendation is either strong or weak. A strong recommendation can be made when consensus clinical expertise is reached, even in the setting of low quality evidence (Box 1).

RESULTS
Giant Cell Tumor
Use of the keywords “Giant cell tumor” and bone revealed 3045 articles. Its association with Denosumab identified 72 articles. Three prospective phase II multicenter clinical trials (six articles) were published (axial and appendicular skeleton GCT). Specific to the spine, one prospective, multicenter study was published and seven case reports. Combination with bisphosphonate yielded 57 articles; one phase II clinical trial and eight retrospective studies. Combination with interferon identified 22 articles with one case report on interferon in recurrent/metastatic GCT of the spine published. Sacral GCT and SAE as a stand-alone treatment had 71 results with six retrospective articles. With preoperative embolization, 67 articles were identified with three studies reporting its preoperative use for spinal GCT (Table 1, http://links.lww.com/BRS/B194).

Aneurysmal Bone Cyst
Use of the keywords “Aneurysmal bone cyst” identified 1546 articles. Regarding doxycycline and ABC, two articles were published. On Denosumab, eight articles were available with three spinal case reports. One hundred four articles on SAE as a stand-alone treatment are published with one multicenter study of 71 patients (17 treated with SAE) and numerous case reports/case series. No dedicated article on preoperative embolization and ABC is available. The use of injectable autologous bone marrow was documented in three articles (Table 2, http://links.lww.com/BRS/B194).

Osteoid Osteoma
Use of the keywords “Osteoid Osteoma” identified 2944 articles. Of those, 10 articles specifically reported the use of thermal ablation for spinal OO (Table 3, http://links.lww.com/BRS/B194).

DISCUSSION
Giant Cell Tumor of the Bone
Intraleosional curettage with the use of local adjuvants is the mainstay of treatment for appendicular GCT and has significantly reduced recurrence rate from 45% to close to 20% in the appendicular skeleton. Their use in the spine is less applicable due to the risk of thermal injury. Recurrence rate is relatively low after en bloc resection in the spine. In 2009, the Spine Oncology Study Group recommended en bloc resection for sacral and mobile spine GCT when feasible. They emphasized, however, that predicted surgical morbidity should be integrated in the decision-making process...
process. Radiation therapy for inoperable GCT was also suggested.

**Role of Medical Treatment**

The multinucleated giant cell is the hallmark of GCT and expresses high levels of the receptor of activator nuclear factor kappa-B ligand (RANKL), an essential mediator in bone resorption. Suppression of osteolysis in multiple myeloma and bone metastases has been demonstrated with Denosumab, a monoclonal antibody that specifically inhibits RANKL. Branstetter et al demonstrated, in 20 patients, a marked reduction of giant cells (up to 90%) but also an increase of new fibro-osseous tissue/woven bone in 65% of the patients. Thomas et al, in a phase 2 clinical trial, evaluated the role of Denosumab in 37 patients with unresectable GCT: 30/35 patients had a favorable tumor response within 6 months of treatment. This led to a larger multicenter prospective phase 2 clinical trial of 282 patients also funded by Amgen. An Interim analysis showed that 163 of 169 patients (63 spine) with “unsalvageable” GCT had no disease progression (median follow-up of 13 months). In a second cohort of 100 patients (seven spine) with salvageable disease, but where anticipated morbid surgery was expected, 74 did not have surgery and 16 of 26 had a less morbid procedure (median follow-up of 9.2 months). Overall, 75% had an objective tumor response (median time to response: 3 months), mostly a partial response. Rutkowski et al published the results of the second cohort. Of 222 patients (21 spine), 48% did not have surgery and 38% had a less morbid procedure than originally planned (mean follow-up of 15.3 months). Of the 116 patients who had surgery, median duration of Denosumab was 14.2 months. Denosumab was continued for six treatments postoperatively. Recurrence rate was 15% (median recurrence time 13.6 months). Ueda et al published on 17 nonsurgical patients who were treated for a median time of 13.1 months with a reported rate of tumor response of 88%. Overall, these studies support Denosumab to control disease progression. However, further research is needed to assess long-term effect, the optimal duration of treatment, and its adjuvant role with surgery.

Currently, the FDA has approved Denosumab for inoperable GCT in adults and adolescents. Administration of calcium and vitamin D to prevent/treat hypocalcemia is recommended. Serious adverse event was reported in 9% with treatment discontinuation occurring in 5% by Chawla et al. Osteonecrosis of the jaw was reported in 1%. Its use in a 10-year-old child had resulted in bony changes similar to osteopetrosis. Lau et al have raised concerns about recurrence after discontinuation of the therapy. As Denosumab does not induce cell apoptosis, the hypothesized mechanism of action is by the blockade of RANKL signaling pathway, and therefore its effect may be reversible after discontinuation. Matck et al reported rapid disease progression after Denosumab cessation. Recently, two case reports on sarcomatous transformation of GCT while on Denosumab were published. This highlights that little evidence is available on long-term use of Denosumab.

Specific to the spine, Goldschlager et al reported the use of preoperative Denosumab in five patients (mean preoperative duration 6 months). All tumors showed radiologic improvement and 25% had histological failure. Intraoperatively, tumor was firmer and dissection was easier to perform. Significant regression of the epidural disease was observed. The neo-adjuvant role of this medication has been reported in only two other studies. Significant tumor reduction was observed in both cases, especially in the paravertebral compartment. In a recent survey of the AOSKFT, 87.51% of the participants reported preoperative use of Denosumab either routinely or on a selected basis. Most common regimen offered was until tumor regression and/or calcification (confirmed by serial imaging modality) or a maximum of 6 months (61.29%), 77.42% of the participants have observed either tumor stabilization or regression. Postoperative Denosumab is not a common practice and may be considered in cases of tumor transgression, recurrence, or intrasional surgery.

**What Is the Role of Denosumab in the Treatment of GCT?**

Denosumab is indicated for the treatment of inoperable GCT (strong recommendation, very low quality evidence). Denosumab is indicated as a neo adjuvant therapy in the treatment of GCT (strong recommendation, very low quality evidence).

Interferon alpha-2B is an antitumoral molecule that causes angiogenesis inhibition. It has been mainly reported in maxillo-facial surgery. Wei et al reported its use in two patients with spinal metastatic, recurrent GCT. Both improved under treatment and showed significant decreased of the tumor’s size. The medication was continued for 3 to 3.5 years. Leucopenia and thrombocytopenia were associated with interferon.

**What Is the Role of Interferon Alpha-2B in the Treatment of GCT?**

We do not support the routine use of interferon in the treatment of GCT (weak recommendation, very low quality evidence).

Bisphosphonates are antiresorptive drugs used in the treatment of osteoporosis and in patients with bony metastases/multiple myeloma. Regarding its role in GCT, multiple in vitro studies have demonstrated apoptosis and inhibition of giant cells with bisphosphonates. Gouin et al conducted phase 2 clinical trial of 20 patients (one sacrum) who received five courses of zoledronic acid postcurettage. At follow-up of 36 months, the recurrence rate was 15%. Yin et al reported a recurrence rate of 13.3% for patient treated with bisphosphonate compared with 48.8% for patient who did not receive it. Bisphosphonate was continued for 2 years postoperatively. Multiple case reports describe successful use of preoperative and postoperative bisphosphonate. Recently, Chen et al...
reported no recurrence at 28 months in four sacral GCT that were treated with curettage and zoledronic acid loaded bone cement. For metastatic disease and recurrent GCT, Balke et al\textsuperscript{41} published on 25 patients (appendicular/sacral) and reported disease progression in only two patients. No guidelines as which molecule/protocol should be employed have been made. Its use is in the treatment of GCT is not currently approved by the FDA.

**What Is the Role of Bisphosphonate in the Treatment of GCT?**

The use of bisphosphonate as an adjuvant for GCT is not recommended (weak recommendation, very low quality evidence).

The use of bisphosphonate in the setting of an inoperable GCT might be considered (weak recommendation, very low quality evidence).

**Role of Interventional Radiology**

Preoperative embolization is widely used in the treatment of metastatic and primary bone tumors. It is associated with reduced intraoperative blood loss and transfusion requirement.\textsuperscript{42–49} Tumor’s size, surgical invasiveness, the completeness of the embolization, the lesion’s vascularity, and the timing between surgery and embolization have an effect on the estimated blood loss.\textsuperscript{43,50–52} Specifically regarding GCT, its use has been reported.\textsuperscript{53–55} Prando et al\textsuperscript{56} reported that 64% of GCTs were hypervascular on angiography. Preoperative embolization is also used to facilitate exposure with easier dissection of the segmental arteries. Finstein et al\textsuperscript{55} reported a complete paraplegia after embolization of a T12 GCT. Localization of the anterior spinal artery should be emphasized when performing these procedures.

Use of selective arterial embolization as a stand-alone treatment for sacral GCT has been reported in small retrospective series.\textsuperscript{57–62} Hosalkar et al\textsuperscript{60} reported stabilization of sacral GCT in seven of nine patients treated with serial embolization (between 3 and 7 SAE). Nakanishi et al\textsuperscript{63} reported successful SAE (mean three treatments) with reossification in three of four patients. Postprocedural neurologic deficit has been reported.\textsuperscript{58,61} Lin et al\textsuperscript{59} observed an objective response in 78% (between 1 and 10 treatments). However, eight of 18 patients required a subsequent surgery. Thangaraj et al\textsuperscript{60} reported mitigated outcomes after SAE in three patients; two required stabilization and the other had recurrence.

**What Is the Role of SAE as Treatment for Spinal GCT?**

Preoperative embolization of hypervascular lesions is indicated in the surgical planning of GCT (strong recommendation, very low quality evidence).

Serial arterial embolization for sacral GCT is not recommended as the primary treatment (weak recommendation, very low quality evidence).

**Aneurysmal Bone Cyst**

ABC can reach considerable size and warrants extensive surgery. In the appendicular skeleton, curettage is supported by the literature and has an acceptable recurrence rate.\textsuperscript{63} After intralesional resection in the spine, recurrence rate has been reported as high as 25%.\textsuperscript{64} Low recurrence rate has been observed with en bloc resection;\textsuperscript{65} however, en bloc resection may not be desirable depending on the location and risk/benefit ratio. The potential morbidity associated with surgical treatments and the significant recurrence rate has led to alternative treatments for ABC.

**Role of Medical Treatment**

GCT and ABC share osteolytic features and Pelle et al\textsuperscript{66} demonstrated similar expression of RANKL between the two on freshly harvested tumors. \textit{In vitro} studies on RANKL expression are conflicting. Taylor et al\textsuperscript{67} concluded that osteoclast-like giant cells in ABC are formed through a RANKL dependent mechanism but Won et al\textsuperscript{68} failed to demonstrate significant RANK expression in ABC compared with GCT. Clinically, Lange et al\textsuperscript{55} reported two cases of recurrent ABC in child that were treated with Denosumab. Tumor regression was observed (follow-up 2–4 months). Skubitz et al\textsuperscript{70} published a case report on a sacral ABC. After a year, tumor regression was confirmed histologically.

**What Is the Role of Denosumab in the Treatment of ABC?**

The use of denosumab in the treatment of ABC is not recommended as a first-line treatment (weak recommendation, very low quality evidence).

**Role of Interventional Radiology**

The role of preoperative embolization has been discussed in the section on GCT. Although no study reports specifically on the effect of preoperative embolization for ABC, it is routinely used. Selective arterial embolization as a stand-alone treatment has been reported. Multiple case report/series have been published on the subject. Amendola et al reported their experience in a prospective study of seven ABC of the mobile spine without instability or symptomatic cord compression. Embolization was repeated as needed (maximum 7). Evidence of tumor response was observed in all patients. Patients with nerve root weakness all improved with SAE. Along with this article, another article reported the use of SAE in the setting of mild neurologic injury (ASIA D) with good results.\textsuperscript{65} A downside to the technique of repeated embolization is radiation exposure to the patient, especially in the paediatric population. In Borjiani’s series, 35% had to have more than six treatments.\textsuperscript{65} Repeated embolization may be due to persistence of feeding vessels or development of collateral flow.

Complications after SAE were rare. Beardsley et al\textsuperscript{78} reported an embolic stroke after embolization of a rib ABC, likely resulting from collateral circulation between the lesion and the vertebral artery. Donati et al\textsuperscript{79} reported persistent glutal pain in sacral ABC. Skin necrosis and
transient paresis has been reported by Rossi et al\textsuperscript{80} but his study included primarily appendicular ABC.

The choice of material utilized for embolization is also important. Particles or acrylic glue is more commonly used. Particles have good penetration and are technically easy to handle. Amendola et al\textsuperscript{91} recommended acrylic glue for permanent SAE, good penetration, and avoidance of the inadvertent distal embolization classically seen with particles. The same authors have successfully reported direct injection of acrylic glue into the cyst after four recurrences with SAE.

**What Is the Role of SAE as Treatment for Spinal ABC?**

Preoperative embolization of hypervascular lesions is recommended in the surgical planning of ABC (strong recommendation, very low quality evidence).

SAE might be considered in the treatment of ABC (weak recommendation, very low quality evidence).

Injection of bone marrow aspirate (BMA) in combination with demineralized bone matrix (DBM) has been reported in three studies.\textsuperscript{79,82,83} Application of BMA and DBM through a minimal incision in 13 patients (no spine) resulted in healing in 11 cases. Appearance of a peripheral shell within 3 months was observed in all successful treatments. The only reported use in the spine is by Donati et al\textsuperscript{79}: one patient whom had failure after SAE was treated with percutaneous injection of BMA and DBM. Progressive ossification was apparent on the 6 and 12 months computed tomography (CT) scan.

**What Is the Role of BMA as Treatment of Spinal ABC?**

Injection of BMA with DBM in the treatment of ABC is not recommended (weak recommendation, very low quality evidence).

Doxycycline is an antibiotic that has shown, on culture, antitumoral proprieties with inhibition of matrix metalloproteinase (MMP), osteoclastic function, and induction of osteoclast apoptosis.\textsuperscript{71–73} ABC expresses high level of MMP.\textsuperscript{74} Bony destruction is associated with upregulation of MMP.\textsuperscript{75} Shiels and Mayerson\textsuperscript{76} published in 2013, a series of 21 ABC (three mobile spine and two sacrum) who received intralesional doxycycline (inoperable lesion, recurrence, or patient’s preference). Eighteen of 21 patients had radiologic improvement. In 2015, a case report was published on a recurrent C2-3 ABC in a 12 yo treated with a single injection of doxycycline.\textsuperscript{77} After 7 months, CT showed complete reossification.

**What Is the Role of Doxycycline in the Treatment of ABC?**

Doxycycline is not recommended in the treatment of ABC as a first-line of treatment (weak recommendation, very low quality evidence).

**Osteoid Osteoma**

Treatment of OO is aimed at relieving severe pain or preventing deformity in children. In the appendicular skeleton, the emergence of thermal ablation has changed the paradigm of treatment and is now considered the gold standard.\textsuperscript{84–86} With these minimally invasive techniques, heat is applied directly to the nidus, usually under CT guidance and with temperature of 90°C for 4 to 6 minutes.\textsuperscript{84,86} In a systematic review, failure of the technique is reported to be 5%.\textsuperscript{87}

**Role of Interventional Radiology**

Concerns about the risk of thermal injury to the neural structure have limited the application of thermal ablation in the spine. In an in vivo study on pigs performed by Nour et al,\textsuperscript{88} ablation directly on the posterior cortex resulted in paraplegia. In another study in an animal model, Bitsch et al\textsuperscript{89} recommended a minimum of 10 mm between the periosteum and neural structure as the temperature decreases below 45°C at that mark. In recent years, thermal ablation has started gaining popularity for spinal OO\textsuperscript{90–99} (Table 4, http://links.lww.com/ BRS/B194). All these studies reported treating OO <10 mm to neural elements with no reports of radiculopathy/paralysis. Caution is recommended by many authors in the absence of cortex between the lesion and the neural structures.\textsuperscript{90,92,93,95–97,99} The absence of cortex does not preclude the technique but mandates protection to neural tissue.\textsuperscript{95,97,99} Thermal protection such as a cooling technique, air insufflation, and epidural irrigation have been described as an additional safety measure.\textsuperscript{91–92,95,97,99} One article by Owen et al\textsuperscript{100} published a unique report on postprocedural fracture of L2 with RFA.

In terms of clinical outcome, cases series on spinal OO report high rates of success between 79 and 100%.\textsuperscript{90–99} The largest study of 58 patients showed a 5.3% recurrence rate.\textsuperscript{97} Vanderschueren et al\textsuperscript{98} observed more failure when the lesion was closer to the neural elements.

**What Is the Role of Thermal Ablation as a Treatment of Spinal OO?**

Percutaneous thermal ablation is indicated for selected OO. Absence of intact cortex and close vicinity <5 mm to neural element warrant precautions (strong recommendation, very low quality evidence).\textsuperscript{101}

**CONCLUSION**

The emergence of alternative and adjuvant therapies for primary benign bone tumors is redefining the way these tumors are treated. Surgery will remain part of the treatment of these lesions, but interventional radiology and medical treatment will be integrated into treatment algorithms. Denosumab is becoming an important factor in the treatment of GCT. Thermal ablation for OO and SAE for ABC are promising avenues for intervention radiology. Further research is needed and their exact role will be clarified over time. Multidisciplinary collaboration is essential to ensure productive high impact research and optimal patient care.
Supplemental digital content is available for this article. Direct URL citations appearing in the printed text are provided in the HTML and PDF version of this article on the journal’s Web site (www.spinejournal.com).

Key Points

- Denosumab is increasingly used in the treatment of giant cell tumor of the bone. It should be used in the setting of an inoperable tumor. Its use as an adjunct to surgery should be considered.
- Selective arterial embolization as a stand-alone treatment of aneurysmal bone cyst has been used with success and can be considered. However, radiation exposure is a concern, especially in the paediatric population.
- Thermal ablation is an effective treatment of osteoid osteoma. Its application to the spinal location appears to be safe in carefully selected cases.

References


