Golden Bullet—Denosumab: Early Rapid Response of Metastatic Giant Cell Tumor of the Bone

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SUMMARY: Giant cell tumor of the bone (GCTB) is usually a benign, locally aggressive tumor with metastatic potential. Histogenesis of GCTB is unknown and a correlation between histologic and clinical course is not recognized. The authors report their case of an 18-year-old girl with a metastatic GCTB to the lungs. Denosumab was initiated empirically. They report 60% to 70% regression of the nodules at 3 months. The patient was back to her daily activities. She is still in the treatment protocol, and we observed 60% to 70% regression on thorax CT just after the third course of the therapy.

DISCUSSION: Histogenesis of GCTB is unknown and has not been found between histologic and clinical course. For this reason, many authors consider its prognosis unpredictable.1,3,5 Lung metastasis after GCTB treatment is well known, and generally has an unfavorable outcome, despite studies with several chemotherapeutic agents,1-6 interferon, and bisphosphonates.1-6 RANKL is highly expressed by the stromal cells within GCTB, consistent with the hypothesis that RANKL expression is responsible for the pathologic recruitment of osteoclast-like cells. The RANKL inhibitor denosumab selectively binds to human RANKL.7,8 Karras et al9 recently presented a 10-year-old girl with patellar GCTB with subcutaneous and multiple pulmonary metastatic nodules. After pathologic diagnosis, she was subsequently started on denosumab without primary surgery. Within 4 months of beginning the treatment, her pain markedly reduced, and 6 to 7 months into treatment she was back to her regular daily activities. On thorax CT, significant regression of the nodules was clearly seen. They also evaluated and showed the desirable histologic response of denosumab.

CASE REPORT

Our patient, a 17-year-old girl, presented with a chief complaint of pain in the right knee. Radiograph and MRI showed an expansile lytic osseous mass in the distal femur (Fig. 1) and there was no metastatic nodule on thorax CT. The pathologic diagnosis of surgical biopsy was GCTB with typical histologic appearance (mononuclear stromal cells along with multinucleated giant cells) (Fig. 2). After diagnosis, curettage and autologous bone grafting surgery were performed. Local recurrence was seen 3 months after primary surgery, and radical surgical resection of the distal femur and application of prosthesis were implemented. One month after the surgery, thorax CT showed bilateral numerous parenchymal pulmonary nodules. Varied chemotherapy regimens (ifosfamide, etoposide, carboplatin, adriamycin, and vincristine) and interferon α-2b were applied, all having failed. Finally, she had chest pain and hemoptysis with huge, progressive metastatic mass on chest CT (Fig. 3). Denosumab has been started, 120 mg per month, subcutaneously with oral vitamin D (400 IU daily), and calcium supplementation (500 mg daily). She did not have hypocalcemia and hypophosphatemia during the treatment period. After 2 doses of denosumab, she had no pulmonary symptoms, and thorax CT showed significant regression (>50%) of the lung mass (Fig. 4). She is still in the treatment protocol, and we observed 60% to 70% regression on thorax CT just after the third course of the therapy. We still need to look for long-term complications (high bone mineral density and osteonecrosis).

Received for publication August 5, 2013; accepted August 23, 2013.

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Chawla and colleagues. He noted that no well-designed studies considering bisphosphonates in GCTB have been conducted, and thus the superiority of denosumab can be only assumed rather than proved. He spotlights the funded study results of Chawla and colleagues to be controversial and calls for independent studies with longer follow-up periods. Otherwise, in the practice of pediatric oncology, it is hard to gather large patient groups together, especially for diseases such as GCTB. Case reports with successful results still have priority and should be considered inevitably to overcome the disease.

Karras et al reported excellent clinical response with denosumab 120 mg, once per week for 3 weeks, followed by 120 mg monthly. We only used 120 mg monthly and we defined rapid objective response after 2 doses.

Denosumab seems to be a well-tolerated drug in the reports. Most common side effects are hypocalcemia, hypophosphatemia, increased bone mineral density, risk for fracture, and osteonecrosis. In our patient, because of decreased bone turnover during denosumab treatment, we used prophylactic vitamin D and calcium supplementation. The patient has had no hypocalcemia or hypophosphatemia, but we still need to look for long-term complications.

In conclusion, we emphasize on early rapid response to denosumab in metastatic GCTB. It is probable that she would require long-term treatment with denosumab, as stated in Karras’ report. What are the long-term response and effects of RANKL blockade in a young? And is

![FIGURE 1. A, Roentgenogram of the right distal femur demonstrates radiolucent expansile lesion with soft-tissue component mass at lower epiphysis-metaphysis region. B, Coronal plane contrast-enhanced fat-saturated MRI of the same lesion was seen as malign radiologic nature with periosteal reaction and soft-tissue mass.](image)

![FIGURE 2. In microscopic evaluation of the tumor, evenly distributed diffuse multinuclear giant cells throughout the cellular stroma were remarkable (hematoxylin-eosin, ×200).](image)

![FIGURE 3. Axial plane thorax CT at the lung window level shows a huge metastatic mass lesion neighboring the heart and aorta, and chest wall. Note that there are numerous metastatic lesion in both the lungs.](image)

![FIGURE 4. After the second course of denosumab therapy, CT reveals significant reduction of metastatic mass.](image)
monthly dosing schedule optimal? These are the questions we would probably answer in the future.

REFERENCES