Collaborative Management of Osteogenic Sarcoma Leads to Best Reported Long-term Survival In Children and Adolescents

Ross Wilkins, MD, Co-Medical Director, The Denver Clinic for Extremities at Risk

Osteogenic sarcoma (OGS) is the most common primary malignancy of bone, occurring most frequently in adolescents with the peak incidence occurring in the second decade of life. The incidence rate for osteosarcoma in U.S. patients under 20 years of age is estimated at 5.0 per million each year. The most common sites are in the metaphyseal region of long bones with 42% occurring in the femur, 19% in the tibia and 10% in the humerus.

Historically, the long-term survival for OGS has been poor. Prior to 1970 survival was less
Best Published Long-term Survival for Kids with Osteosarcoma

- 93% 10-year overall survival rate for pediatric patients age (62 patients, ages 7 – 21 years)
- 84% event-free survival
- 93.5% of the 62 patients underwent limb preservation surgery

All patients underwent the intra-arterial chemotherapy protocol developed by the clinicians of The Denver Clinic for Extremities at Risk at Rocky Mountain Hospital for Children®.

The limited gains in survival utilizing conventional chemotherapy protocols for treatment of OGS led the physicians of The Denver Clinic for Extremities at Risk at Presbyterian/St. Luke’s Medical Center and Rocky Mountain Hospital for Children® to develop a new chemotherapy protocol for treatment of bone cancer.

Normal tissues receive as much drug as the diseased tissues.

Because large dogs are diagnosed with osteosarcoma at a much higher rate than humans, and the Animal Cancer Center at Colorado State University specializes

<table>
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<th>The Denver Clinic for Extremities at Risk Clinical IA Chemotherapy Trial Results</th>
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<tr>
<td><strong>Pediatric (7 – 21 years)</strong>^4^,^5^,^6^</td>
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<tr>
<td><strong>Total number</strong></td>
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<tr>
<td><strong>Tumor type</strong></td>
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<td>≥90% tumor necrosis</td>
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<td><strong>Event-free survival</strong></td>
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<td><strong>10-year overall survival</strong></td>
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The Denver Clinic is utilized on pediatric patients. At the time of the first treatment, an arteriogram is obtained for comparison purposes and to plan placement of the catheter. The protocol requires an

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induction dose of IV Doxirubicin over a 48-72 hour period, followed by an intra-arterial dose of Cisplatin infused directly into the tumor. This is repeated every 21 days until one of these three criteria are met:

1) ≥ 90% decreased neo-vascularity, or
2) no serial response (plateau of effect), or
3) there is progression of disease.

Once optimal response is achieved the patient undergoes surgical resection and the tumor is analyzed by pathology to determine actual tumor necrosis. If the specimen shows ≥ 90% necrosis the patient is categorized as a “good responder” and undergoes a post-operative course of Adriamycin and Cisplatin for 2 to 3 cycles. If the patient is determined to be a “non-responder” (<90% tumor necrosis) he or she will undergo a longer six-cycle post op course alternating between high dose ifosfomide and methotrexate.

The Denver Clinic for Extremities at Risk has published the results of the clinical trial for pediatric patients treated utilizing the intra-arterial chemotherapy protocol. Results are shown in the table (see page 2).

Our regimen has continued to demonstrate considerably improved survival when compared with other published results for treating primary non-metastatic extremity OGS in children.

Using Kaplan-Meier statistical methods, the 10-year survival for pediatric and adolescent patients is 93% and event-free survival is 86%.6 Another center’s study on IA chemotherapy for nonmetastatic osteosarcoma reported that 56% of patients (n=43, all ages) had greater than 90% tumor necrosis but an overall survival rate of 68% at seven years and 53% event-free survival at seven years.7

The collaboration of the physicians of The Denver Clinic for Extremities at Risk has led to significant survival benefits for kids diagnosed with osteogenic sarcoma. This patient-centered approach has been the hallmark for all service lines at The Denver Clinic, allowing patients and families to experience “uncommonly good care” for any type of extremity tumor. ■


LJ was an otherwise healthy 15-year-old boy when he developed right knee pain while on vacation in July of 2007. An x-ray showed a sclerotic lesion within the metaphysis of the proximal tibia (Fig. 4). He was referred to Dr. Ron Hugate at The Denver Clinic for Extremities at Risk for evaluation.

MRI (Fig. 5) and x-ray findings were suspicious for osteosarcoma of the tibia. Open biopsy confirmed the diagnosis of high-grade osteosarcoma. Staging studies were completed and a CT scan of the chest showed a mass. He underwent a thorascopic biopsy of the lung nodule which was read as benign with no evidence of malignancy.

LJ was treated with intra-arterial Cisplatin according to the treatment protocol developed by the physicians of the Extremities at Risk program. After his fourth course of chemotherapy, the team of medical oncologists, orthopedic oncologists, and interventional radiologists felt he had greater than 90% tumor response on serial arteriography (Figs. 6 - 9) so the resection and reconstruction procedure was planned.

In October of 2007, he underwent a surgical resection followed by reconstruction using a custom, trabecular metal proximal tibial replacement with a hinged knee (Fig 10). The trabecular metal was utilized to provide a mechanism to encourage tendon adhesion to the prosthesis and improve his extensor mechanism function. Due to the extent of the resection, a soft tissue reconstruction was necessary so...
Dr. Conrad Tirre utilized a medial gastrocnemius flap and split-thickness skin graft for coverage. Histologic analysis of the tumor specimen showed 95% necrosis of the tumor and negative margins. JL underwent post-operative chemotherapy, according to the treatment protocol, consisting of six cycles of intravenous methotrexate, etoposide and docetaxel. He tolerated the chemotherapy without complications.

At his one-year follow-up his passive knee motion was zero to 120 degrees but he had a 30-degree extensor lag. In December 2008, the patient underwent surgery to advance his extensor mechanism and improve his active extension. He did well after surgery with an improved gait and equal limb lengths. Six weeks post-op, he was able to fully weight bear with the use of a knee immobilizer and had no extensor lag. His strength steadily improved to the point he no longer utilizes any assistive device or knee support and has no functional deficits. He is currently enrolled at Johns Hopkins University majoring in biomedical engineering and spending his free time “traveling the world”.

The Denver Clinic for Extremities at Risk was established in 1986 to provide specialty care to kids and adults with complex orthopedic problems. Located on the campus of Rocky Mountain Hospital for Children® at P/SL, The Denver Clinic’s pediatric services include management of bone and soft tissue tumors of the extremities and spine, surgical management of extremity deformity and bone healing problems, hip preservation procedures, and amputation services. Our specialists are available for consultation about patients with complex orthopedic problems through our referral line, 1-800-262-5462.

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(Joining April 1, 2013)
ST was a healthy and active 17-year-old male student when he sustained a pathologic fracture of his right radius while playing football in November 2006. Prior to the injury, the patient noted discomfort in his right forearm just below the elbow, especially when playing football (Fig. 11). He was seen in a local emergency department where he was admitted for evaluation.

He underwent an open biopsy at the time which proved consistent for Ewing’s sarcoma. His metastatic work-up was negative for metastatic disease.

He started treatment for Ewing’s Sarcoma and the hospital the where he initially presented. He completed two cycles of vincristine, doxorubicin, and cyclophosphamide. The family sought a second opinion from Dr. Ross Wilkins at The Denver Clinic for Extremities at Risk after they were presented with surgical options.

Following evaluation by Dr. Wilkins, ST’s case was presented at the weekly Denver Clinic multidisciplinary conference to discuss his reconstruction options. Options discussed included amputation, a one-bone forearm allograft, and a free fibula bone transfer. All options were presented to the patient and his parents, including possible complications and functional expectations. Because the patient was highly active and had future plans of pursuing involvement in golf, it was decided to reconstruct his forearm utilizing an allograft bone transplant. The family decided to transfer care to The Denver Clinic for Extremities at Risk and in addition to surgery, complete chemotherapy with the pediatric oncologists with the Extremities at Risk program. He completed two cycles of pre-operative chemotherapy under Dr. Lorie Odom’s care.

He underwent resection and reconstruction in January 2007. Dr. Wilkins and Dr. David Schnur, plastic surgeon, resected the involved section of the radius and completed a neurolysis and tenodesis of the brachioradialis and extensor carpi radialis brevis. An allograft radius obtained from AlloSource (Centennial, CO) was fixed to a locked plate so that the patient would have excellent restoration of anatomy (Fig. 12). Post-operatively, he completed eight courses of chemotherapy incorporating cytoxan, doxorubicin, ifosfamide/mesna, etoposide, temozolomide, and irinotecan.

Two months after surgery he had no pain and full range of motion of his wrist, forearm and elbow with evident callus at each end of the allograft. Five months after surgery, the x-ray showed solid union of the allograft to the radius at the proximal and distal ends.

Two years later, ST completed professional golf school in San Diego. He had no signs of recurrence, satellite lesions or lymphadenopathy. The allograft was well healed. He is over five years out from his initial diagnosis and is a professional golf instructor in Florida.
An MRI revealed a large soft tissue mass that was closely approximated to the artery and nerve (Fig. 13). A biopsy confirmed the diagnosis of alveolar rhabdomyosarcoma. A metastatic workup was negative.

He underwent resection of the mass but the surgical margins were positive so his case was discussed at The Denver Clinic for Extremities at Risk weekly patient conference. The options of an above-knee amputation, knee disarticulation, or a four- to five-week course of radiation were considered. The decision was made to proceed with a knee disarticulation because of the ability to achieve clean margins with a knee disarticulation as well as the concern for growth disturbance that radiation could produce. Moreover, radiation therapy would not improve long-term survival.

He underwent a knee disarticulation. Margins were negative and his metastatic workup remained negative as well.

Approximately one month after surgery, he was started on chemotherapy consisting of vincristine, actinomycin, cytoxan, and topotecan under the direction of Dr. Zimbelman. About three months post-op, he had a well-healed surgical incision over his stump and was thriving and walking, utilizing a prosthesis.

Two years later, a soft tissue lesion around the sciatic nerve was seen. He underwent a wide resection of the left posterior thigh mass which was consistent with a sciatic nerve fibroma.

As of April 2012, he continues to be disease-free and is thriving. He is now in third grade and is active in a variety of sports including wrestling. He continues to wear his prosthesis for all activities, requiring regular revisions due to physical changes associated with normal growth. He is followed annually by both Dr. Kelly and Dr. Zimbelman to assess for any change in disease status.

Rocky Mountain Pediatric Hematology Oncology Practice

Rocky Mountain Pediatric Hematology Oncology is a practice with four board-certified physicians in pediatric hematology and oncology care, pediatric oncology nurses and support staff, who provide a complete range of options for cancer diagnosis, treatment and follow-up.

Through Rocky Mountain Hospital for Children® at P/SL the cancer program provides infusion services for administration of chemotherapy, biotherapies, antibiotics, or medicines for treating a wide range of cancer and hematologic disorders.

These combined services and a team approach provide patients and their families the benefit of advanced medical training and research in a highly supportive private practice where patients receive personalized care.

Services
The team at Rocky Mountain Pediatric Hematology Oncology provides inpatient and outpatient diagnostic evaluation and treatment for the full spectrum of pediatric cancers and blood disorders through Rocky Mountain Hospital for Children® at Presbyterian/St. Luke’s Medical Center.

Our team of pediatric cancer specialists provides consultation and medical management for infants, children, adolescents and young adults with cancer, blood disorders, benign tumors, and suspected malignancies.

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Clinical Research
Rocky Mountain Pediatric Hematology Oncology is a member of the Children’s Oncology Group, a worldwide clinical trial cooperative group supported by the National Cancer Institute (NCI).

The mission of COG is to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care.

This relationship allows Rocky Mountain Hospital for Children® to collaborate on clinical research with other investigators from across the country and in some foreign countries and to bring clinical advances to benefit treatment for our patients.

Contact Us
For consultation or patient referral, please call 303-832-2344.

Pediatric Cancer
these difficult tumors has been possible only because of the close cooperation and collaboration among members of a diverse health care team, including the pediatric oncologists, the orthopedic oncologists, the pathologists and the interventional radiologists at Presbyterian/St. Luke’s Medical Center and Rocky Mountain Hospital for Children®. There currently plans for additional modifications and improvements in the evaluation, treatment and long-term follow-up of these primary bone tumors. This edition of the newsletter reviews the current concepts and case examples involved with pediatric extremity malignancies.

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