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

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. A second incidence peak occurs after 60 years of age. Incidence rates for osteosarcoma in U.S. patients under 20 years of age are estimated at 5.0 per million per 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 than 20%. With advances in chemotherapy agents and protocols survival improved to 40–50% in the 1970s and to 50–70% in the 1980s. Best reported 8 to 10 year survival for patients undergoing IV chemotherapy for treatment has been 61–72%1, and 5 year survival being 73–74%1. These protocols deliver preoperative chemotherapy intravenously with no adjustment in dose or duration for larger tumors. With the IV protocols, multiple drugs (three or more) are utilized which have additive toxicities therefore limit the dose intensification of any one drug. There is no accurate method to monitor ongoing tumor necrosis and normal tissues receive as much drug as the diseased tissues.

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 The Rocky Mountain Hospital for Children to develop a new chemotherapy protocol for treatment of bone cancer.

Large dogs are diagnosed with osteosarcoma at a much higher rate than humans, and the Animal Cancer Center at Colorado State University specializes in treatment. Through the translational research projects with CSU, a team of adult and pediatric medical oncologists, orthopedic oncologists, interventional radiologists, and pathologists sought to develop a protocol that utilized the most effective agents without the cross toxicities, delivered a high concentration of the chemotherapy agent directly to the tumor, increased the dose for larger (>10cm) tumors, and provided feedback regarding tumor response to allow for optimal timing of surgery.

The intra-arterial (IA) chemotherapy protocol developed by the physicians of The Denver Clinic is utilized on pediatric and adult 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 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 6-cycle post op course alternating between high dose ifosfamide and methotrexate.

The Denver Clinic for Extremities at Risk has published the results of the clinical trial for pediatric and adults treated utilizing the intra-arterial chemotherapy protocol. Results are shown in the table.

Denver Clinic for Extremities at Risk Clinical IA Chemotherapy Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Pediatric (7 – 21 years)</th>
<th>Adult (18 – 77 years)</th>
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</thead>
<tbody>
<tr>
<td>Total number</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Tumor type</td>
<td>Non-metastatic osteogenic sarcoma</td>
<td>High grade osteogenic sarcoma and MFH of bone</td>
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<td>&gt;90% tumor necrosis</td>
<td>41 good responders (87%) 6 non-responders</td>
<td>41 good responders (77%) 12 non-responders</td>
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<tr>
<td>Event-free survival</td>
<td>84%</td>
<td>79%</td>
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<tr>
<td>10-year overall survival</td>
<td>92%</td>
<td>82%</td>
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Our regimen has continued to demonstrate considerably improved survival when compared with other published results for treating primary nonmetastatic extremity OGS in children and adults. Using Kaplan–Meier statistical methods, 82% of adult patients treated on this regimen are projected to survive 10 years and 79% will remain continuously disease-free5, 6. This compares with the breakout of pediatric and adolescent patients treated on this IA protocol who had 10-year survival of 93% and event-free survival of 86%6, 7. In another center’s study on IA chemotherapy for nonmetastatic osteosarcoma, they reported that 56% of patients (n=43, all ages) had greater than 90% tumor necrosis but overall survival was 68% at 7 years and 53% event free survival at 7 years8.

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

CASE #1 – LJ

TI'BAL OSTEOSARCOMA

PHYSICIANS

Ronald Hugate, MD; orthopedic oncologist
Jennifer Clark, MD; pediatric oncologist
Conrad Tirre, MD; plastic surgeon

HISTORY

LJ was an otherwise healthy 15 year old 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. 1). He was referred to Dr. Ron Hugate at The Denver Clinic for Extremities at Risk for evaluation. MRI (Fig. 2) 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 thoracoscopic 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. 3 – 6) 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 7). 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. LJ underwent post-operative chemotherapy, according to the treatment protocol, consisting of three cycles of intravenous methotrexate, etoposide and docetaxel. He tolerated the chemotherapy without complications.

At his one year follow-up his passive knee motion was 0 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”.

CASE #2 - ST
EWING SARCOSTMA

PHYSICIANS
Ross Wilkins, MD; orthopedic oncologist
Lorie Odom, MD; pediatric oncologist
David Schnur, MD; plastic surgeon

HISTORY
ST was a healthy and active 17-year-old male student when he sustained a pathologic fracture of his right radius in November 2006 while playing football. Prior to the injury, the patient noted discomfort in his right forearm just below the elbow, especially when playing football (Fig 8). 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 Ewings sarcoma. His metastatic work-up was negative for metastatic disease.

He started treatment for Ewing Sarcoma at the hospital the where he initially presented. He completed two cycles of vincristine, doxorubicin, and cyclophosphamide. The initial treating physician recommended amputation so the family sought a second opinion from Dr. Ross Wilkins at The Denver Clinic for Extremities at Risk.

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, an 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 sports, 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. Lorraine Odom’s care.

ST underwent resection and reconstruction in January 2007. Dr. Wilkins and Dr. David Schnur resected the involved section of the radius and completed a neurolysis of the major nerves and tenodesis of the brachioradialis and extensor carpi radialis brevis. An allograft donor radius obtained from Allosource (Centennial, CO) was fixed with a locked plate so that the patient would have excellent restoration of anatomy (Fig. 9). Post-operatively, he completed the Ewing Sarcoma protocol of chemotherapy incorporating cytoxan, doxorubicin, ifosfamide/mena, 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 now over five years out from his initial diagnosis and is a professional golf instructor in Florida.

CASE #3 - ST
RHABDOMYOSARCOMA

PHYSICIANS
Cynthia Kelly, MD; orthopedic oncologist
Julie Zimbelman, MD; pediatric oncologist

HISTORY
This young man presented to the physicians with The Denver Clinic for Extremities at Risk over 8 years ago when he was a 9-month-old. His parents noticed that his left calf was swollen but it did not to cause him any pain or distress. An MRI revealed a large soft tissue mass that was closely approximated to the artery and nerve (Fig 10). A biopsy confirmed the diagnosis of alveolar rhabdomyosarcoma. A metastatic work-up 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 4 - 5 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 with that radiation could produce. In addition, radiation therapy would not improve long term survival.

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

Approximately 1 month after surgery, he was started on chemotherapy consisting of vincristine, actinomycin, cytoxan, and topotecan under the direction of Dr. Zimbelman. About 3 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 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. He is followed annually by both Dr. Kelly and Dr. Zimbelman to assess for any change in disease status.
The 2nd annual Laughs to Save Limbs and Lives benefiting The Limb Preservation Foundation was held on April 20, 2012 at the Paramount Theatre in Denver, Colorado. The event raised a net of $120,000, making this one of the organization's most successful events yet. The evening featured laugh out loud comedians, delicious food and spectacular auctions. Three local acts performed, including Dan McGowan. McGowan was featured on NBC's “Last Comic Standing. The emcee for the event was patient and upcoming motivational speaker, Woody Roseland.

All funds raised go to support the mission of The Limb Preservation Foundation to enhance the quality of life for individuals facing limb-threatening diseases due to trauma, tumor or infection. One of the primary goals of The Foundation is to provide patients with access to the best health care and to eliminate financial burdens, which allows the patient and their family to focus on healing.

The Patient Assistance program provides financial reimbursements for uninsured and under-insured patients through subsidiary programs that include the Patient Service Fund, the Medical Transport Fund, Emergency Distress Fund, Caregiver Lodging Fund and the Durable Medical Equipment Loan Program.

A young teenage girl was recently diagnosed with osteosarcoma. Physicians found a tumor in her right tibia and she is currently being treated by the expert medical team at the Denver Clinic for Extremities At Risk. Her mother, a single parent, is unable to work to care for her daughter as she begins her recovery journey. Travel for surgery, doctor appointments and subsequent chemotherapy is costly. The Limb Preservation Foundation wants her to focus on healing and have family support during the process. To ensure this family gets the care they need, the Patient Assistance Program funded gas and food cards for this young lady and her family during this difficult time.

Funds raised from the Laughs to Save Limbs and Lives event assist patients like this going through traumatic circumstances. The Limb Preservation Foundation extends a sincere thanks to all event participants, including the physicians of the Denver Clinic for Extremities At Risk, for their genuine concern for the clients they serve.

Denver Clinic for Extremities At Risk Drs. Brown, Kelly and Wilkins donate their cooking skills to raise funds for The Foundation. Pictured are Dr. William Brown, Dr. Cynthia Kelly, Jon Schutz, and Sandie Brown.