DR. CAROLA ARNDT: I'm Dr. Carola Arndt, professor of pediatrics in the Division of Pediatric Hematology/Oncology in the Department of Pediatrics at Mayo Clinic. Today I'm going to discuss the review article that will be coming out in an upcoming issue of *Mayo Clinic Proceedings* on common musculoskeletal tumors of childhood and adolescence.

Even though the title is "Common Musculoskeletal Tumors," these tumors are actually quite rare in children, as malignancies are rare in children. However, they are the most common musculoskeletal tumors and comprise Rhabdomyosarcoma, Ewing Sarcoma, and Osteosarcoma. And these tumors have an incidence of somewhere between three and five per million children. They're usually diagnosed in younger children, in toddlers, the peak incidence for Rhabdomyosarcoma, and teenagers and young adults for Osteosarcoma and Ewing Sarcoma.

The signs and symptoms of bone tumors are usually pain and swelling in a joint or extremity or in the case of Ewing's, which has a higher incidence in the pelvis, pelvic pain or back pain. And because Rhabdomyosarcoma can arise pretty much anywhere in the body, the signs and symptoms depend on where the primary tumor is. For example, patients may present with urinary retention if they have a bladder prostate tumor or a mass on an arm or leg if they have an extremity Rhabdomyosarcoma.

Probably one of the most important take-home messages of this review article is that multidisciplinary care is extremely important in providing the best cure rate and the best long-term outcome for these patients. And the multidisciplinary approach really involves participation of the pathologist in making the best diagnosis. Oftentimes in difficult cases, that will include molecular diagnoses using RT PCR or FISH techniques to look for characteristic chromosomal translocations.

It involves the pediatric oncologist or medical oncologist, who usually serves as the conductor or director of the multidisciplinary team approach, as well as inclusion of the surgeon and the radiation oncologist, so that there's truly a multidisciplinary approach in treating these patients and affording them the best opportunity for cure, with the lowest risk of long-term effects.

The other highlight of this review article is the pivotal role that has been played by clinical trials in treatment of these sarcomas. And the Ewing Sarcomas have a long track record of clinical trials over the years, as does Osteosarcoma and Rhabdomyosarcoma. Now, sometimes clinical trials improve the outcome of patients, and sometimes if they're randomized clinical trials, there's actually no difference in outcome.

However, the most recent clinical trial for Ewing Sarcoma as an example, which randomized patients to receive therapy every two weeks versus every three weeks with the same doses of chemotherapy, showed a significant improvement in outcome in those patients who were treated with every-two-week treatment as opposed to every-three-week treatment.

Similarly for patients with Rhabdomyosarcoma over the years, the outcome for patients with good risk, favorable histology, low-stage disease, their outcome has risen to over 90% cure rate for that particular risk group. The converse in patients with poor risk disease, unfortunately, clinical trials have not improved the outcome of patients with the highest risk metastatic Rhabdomyosarcoma or the highest risk Ewing Sarcoma. However, it really is through clinical trials that we will learn and can try new therapeutic approaches to see if they make a difference in being able to make some headway in curing these patients.

Probably the most exciting areas that have come up in the past couple of years is the identification of molecular targets, which are now being utilized in upcoming clinical trials, which hopefully will ultimately improve the outcome of patients with high-risk as well as low-risk disease. Some of these molecular targets include the mammalian target Rapamycin, an inhibition of mTOR.

Another target is the insulin growth factor receptor and targeting that with insulin growth factor receptor inhibitors, because many of these tumors-- actually all of these tumors express IGFR. And so targeting IGFR with IGFR inhibitors has become a goal of some trials coming down the pike. Inhibition of angiogenesis with multiangiogenesis inhibitors, such as vasculo endothelial growth factor inhibitors and similar inhibitors of those molecular targets is also being explored really in treatment of all of these childhood and young adult sarcomas.

In addition, new radiation techniques, specifically and most excitingly the use of proton beam therapy are being more and more widely used, specifically in those centers that have proton beam therapy, and the hope is that the new techniques of radiation therapy-- proton beam therapy or stereotactic body radiotherapy, which is highly conformal radiotherapy. So use of these techniques hopefully will not only improve the percentage of local tumor control, but hopefully will also significantly decrease the risk of late effects, which are not inconsequential in these patients, especially when they're treated at a young age.

Proton beam therapy can significantly target the tumor, while minimizing so-called collateral damage or damage to adjacent normal structures, and so the hope is that proton beam radio therapy will decrease second malignancies as well as decrease damage to surrounding tissues that lie close to the tumor. Surgery techniques are also evolving, and there are always newer limb salvage techniques being developed. Even for those few patients who require amputation-- and fortunately that really is the minority of patients-- there are new prostheses being developed to help patients who cannot avoid amputation.

Since we've now been better at curing many of these patients, we now have to deal with the late effects of treatment, and these are not inconsequential. Patients who received anthrocyclines for treatment of their malignancies have a higher risk of having cardiac toxicity. Patients who have had radiation to other areas in the body may have endocrine late effects. The ovaries or the testicles may have been included in the radiation field, leading to unavoidable ovarian or testicular failure.

Second malignancies can be caused by radiation or chemotherapy. Hearing loss can be caused by platinum. So the-- there is also a big emphasis on trying to find ways to modulate late effects and also an emphasis on understanding the late effects and monitoring the long-term survivors for development of these late effects and making sure that whichever providers care for these patients once their chemotherapy is finished, be it the pediatric oncologist, be it the medical oncologist, be it survivorship clinics, be it pediatricians, family practice physicians, internal medicine physicians-- whoever follows these patients should be aware of the potential long-term effects, and patients should be provided, at the end of their treatment, with a summary of the therapy that they've received. And there are also survivorship guidelines which have been made available for anyone on the internet.

In conclusion, the majority of patients with nonmetastatic childhood musculoskeletal tumors, specifically Rhabdomyosarcoma, Ewing Sarcoma, and Osteosarcoma that's nonmetastatic can be cured. As I mentioned, for favorable risk, nonmetastatic, low-stage, favorable histology Rhabdomyosarcoma, the outcome for those patients is probably in excess of 90%.

For patients with Ewing Sarcoma that's nonmetastatic, the five-year event for survival is probably in the realm of 70% to 75%, similarly for Osteosarcoma. Unfortunately, for patients with metastatic disease, the outcome still remains much to be desired, and those patients have outcomes of well under 50%. And hopefully in those patients exploitation of the molecular targets that are being better understood will provide some hope in the future for better outcomes.

Also, for those patients with very good outcomes, we are hoping to be able to decrease intensity of therapy and decrease the late effects. And in addition, there is much more awareness nowadays of what late effects need to be watched for and how patients need to be monitored for development of late effects following cure of their cancer. Thank you very much.

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