

# CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

## Targeted Treatment in Sarcoma Patients

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### **H&O** How has the treatment of sarcomas evolved?

**DL** Over the last several decades, we have gone from treating sarcoma with just surgery, to the introduction of radiation, to the recognition that chemotherapy is beneficial to many sarcoma patients. We have now entered the era of targeted treatments, such as the discovery of imatinib (Gleevec, Novartis) for patients with gastrointestinal stromal tumors. At present, we are attempting to replace the more generic untargeted treatments, like standard chemotherapy drugs (doxorubicin and ifosfamide), with targeted therapies, like antibodies against the insulin-like growth factor receptor 1 (IGF1R) and kinase inhibitors (ie, imatinib). However, this is still in its infancy in sarcoma. There have been several examples of targeted therapy showing efficacy and many more examples of targeted therapies not yet reaching their promise. At present, we are still trying to understand why certain drugs work in one subset of sarcoma patients but not in another subset.

### **H&O** Why is there a lag in the development of targeted agents in sarcoma?

**DL** I think the lag stems from a slower pace of research, which is based on the fact that sarcomas are rare. Much more is understood about the biology of the more common tumor types like breast cancer and colorectal cancer; they tend to attract larger research funding because

investigators are interested in treating diseases that affect larger numbers of people. It is easier to justify supporting research aimed at a disease that affects 1 in 10 adults compared to one that affects 10,000 people per year. The rationale behind these targeted therapies is to recognize physiologic differences between tumor and non-tumor cells. The introduction of targeted therapies has to wait until the biology of the tumor is understood, and the biology research in sarcomas lags behind the biology of other tumor types.

### **H&O** How can we overcome the challenges seen in drug development?

**DL** The biggest challenge is figuring out a way to improve the research support aimed at sarcoma. I think this will require a better recognition across the oncology community of the existence of basic principles underlying the development of cancer cells that apply regardless of the kind of tumor being studied. Therefore, there is a value in studying rare tumors such as sarcoma, as they may shed some light on the important principles of cancer biology as a whole.

### **H&O** Can you discuss the different types of targeted therapies?

**DL** Generally speaking, there are therapies that are aimed at molecules that are expressed on the surfaces of cells externally, such as monoclonal antibodies directed against IGF1R. They act in various ways: some bind to cell surface receptors and block the ligand from binding to the receptor, some bind to the cell surface receptor and speed internalization (ie, removal from the surface

of the cell), and some bind to the cell surface receptor and activate it. In the case of blocking ligand binding and speeding internalization, the net effect is similar: preventing ligand from activating the receptor.

Moving into the cell, there are targeted therapies that block kinases, either tyrosine kinases, which are usually the signaling part of the membrane-bound receptor, or intracellular kinases that mediate the signal transducing from the membrane to the nucleus. These are usually, but not always, inhibitors of ATP binding in the catalytic part of the kinase. Imatinib is a good example of this type of targeted therapy.

Moving further into the nucleus, drugs are being developed that interfere with the function of transcription factors, either by interfering with their ability to bind to their targets in DNA or interfering with their ability to interact with each other or with proteins that are important for their function. These targets are much further behind in development because of various technical obstacles. It is easiest to treat a cell with a drug that is going to function outside of the cell because the molecule does not have to penetrate the cell. Following this in level of difficulty is a molecule that works in the cytoplasm; here it is necessary to figure out how to get the drug into the cytoplasm (ie, crossing 1 membrane). Getting a molecule into the nucleus is a lot more challenging because the drug needs to cross the cytoplasmic membrane, penetrate the cytoplasm, and cross the nuclear membrane (ie, crossing 2 membranes).

### H&O What are some ongoing studies evaluating targeted treatments in sarcoma?

**DL** There were a slew of recently completed studies that looked at IGF1R antibodies in sarcomas. The results of 2 of these studies were recently published in the *Journal of Clinical Oncology*. The studies had mixed results; some patients seemed to benefit dramatically while others did not. We are now trying to understand what distinguishes the tumors that responded from those that did not respond.

The SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) trial is a recently completed study that looked at the mammalian target of rapamycin (mTOR) inhibitor ridaforolimus, which was administered as maintenance therapy for patients with soft tissue sarcoma. There is also a study, for which we were accruing patients, that was designed to evaluate the ability of temsirolimus (Torisel, Wyeth) to reverse the chemoresistance of sarcomas that were either recurrent or refractory. Patients were given the

combination of temsirolimus and liposomal doxorubicin with the idea that by interfering with mTOR inhibition of AKT, temsirolimus would make chemotherapy refractory cells sensitive to the liposomal doxorubicin. This trial has been halted due to the national shortage of liposomal doxorubicin.

The Children's Oncology Group is conducting a similar study in patients with recurrent rhabdomyosarcoma. In this trial, patients are receiving either bevacizumab or temsirolimus in combination with chemotherapy. Finally, throughout the pediatric and adult groups, there are early-phase trials of small-molecule inhibitors of various kinases that are aiming to determine which of these may be useful for sarcoma patients.

### H&O Can you talk about your research in cancer stem cells?

**DL** Our lab has been working on identifying and targeting Ewing sarcoma stem cells. The data we published last year showed that Ewing sarcoma stem cells can be identified based on their high levels of expression of aldehyde dehydrogenase, which is an enzyme that is important for detoxification of many environmental toxins. Aldehyde dehydrogenase is also important for breaking down cyclophosphamide and ifosfamide. Our work subsequent to that has focused on identifying ways to kill these cells that are otherwise resistant to standard chemotherapy. Our clinical trial of temsirolimus and liposomal doxorubicin, mentioned above, was based on some of our laboratory findings that suggested that it is possible to overcome the chemotherapy resistance of the Ewing sarcoma stem cells using an mTOR inhibitor. Our data also showed that a molecule developed by Dr. Toretsky and colleagues at Georgetown University that targets EWS-FLI1, which is a transcription factor resulting from the chromosome translocation that underlies Ewing sarcoma, is proving to be toxic to Ewing sarcoma stem cells that are resistant to standard chemotherapy.

### Suggested Readings

Awad O, Yustein JT, Shah P, et al. High ALDH activity identifies chemotherapy-resistant Ewing's sarcoma stem cells that retain sensitivity to EWS-FLI1 inhibition. *PLoS One*. 2010;5:e13943.

ClinicalTrials.gov. Vinorelbine Ditartrate and Cyclophosphamide in Combination With Bevacizumab or Temsirolimus in Treating Patients With Recurrent or Refractory Rhabdomyosarcoma. <http://clinicaltrials.gov/ct/show/NCT01222715>. Identifier: NCT01222715.

Liddy Shriver Sarcoma Initiative. Targeted therapies for sarcomas: the next generation of treatments. [http://sarcomahelp.org/research\\_center/targeted\\_therapies.html](http://sarcomahelp.org/research_center/targeted_therapies.html).