

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Agents for Sarcoma

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H&O What are the unique challenges of treating sarcoma?

LB Sarcomas present a challenge for two reasons. First, they comprise a relatively uncommon group of diseases, with at most 15,000 cases each year in the United States, which is a small fraction of the number of cases of breast or prostate cancer each year. More complicated is the fact that sarcomas represent many diseases, not a single entity. In sarcomas, we now know there are 50 or more histologic subtypes. Some sarcomas begin in the body's soft tissues, whereas others begin in the skeleton, and there are remarkable differences between the two. Most cancers occur in older populations, but sarcomas occur in several populations, including newborns and young children, teenagers and young adults, and middle-aged and older adults. Thus, unlike with most cancers, medical and pediatric oncologists must work together in developing treatment strategies for sarcomas occurring across age groups. Further, because of the number of different primary sites of sarcoma, several surgical disciplines are involved in the diagnosis and/or treatment of this heterogeneous but uncommon malignancy, including general, thoracic, and head-and-neck surgeons; surgical and orthopedic oncologists; urologists; and neurosurgeons.

With regard to drug development, Dr. Richard Pazdur of the US Food and Drug Administration (FDA) has recently noted that sarcoma or other uncommon cancers cannot be held to the same standard as a more common cancer would be held; the largest trial, for

example, of adjuvant chemotherapy in patients with sarcoma included approximately 500 patients, whereas to demonstrate benefit of adjuvant chemotherapy in breast cancer or colon cancer trials, the recruitment of thousands of patients is planned and executed. Clearly, accruing large numbers of patients with sarcoma for a phase III trial poses a great challenge. Sarcoma therefore lends itself to innovative ways of looking at clinical benefit. For example, researchers have been successfully able to defend strategies that assess progression-free survival as a primary endpoint in this setting, and the FDA has accepted this strategy on two occasions in part because of the relative rarity of the cancer, as well as its complexity.

H&O Could you discuss how sarcoma has served as a paradigm for development of therapies for other cancers?

LB It is historically accurate to say that sarcoma clinicians, particularly orthopedic oncologists, taught all oncologists that it is not necessary to amputate to obtain cure. In the early 1970s, a patient with an extremity osteosarcoma or Ewing sarcoma was amputated. The surgeons were greatly concerned about amputating young patients who would eventually go on to die anyway, so they then began to think about other treatment options. Around the same time, pediatric and medical oncologists started to use chemotherapy to treat these diseases. Thus, the treatment of osteosarcoma and Ewing sarcoma with chemotherapy and limb-salvage surgery evolved. In the early 1970s, a woman with breast cancer was surgically treated with amputation of the breast (mastectomy), and later on, surgeons and radiation oncologists began to consider the use of lesser surgery on the model of limb-salvage surgery in order to preserve the breast.

Additionally, from the perspective of molecular biology, approximately 40% of sarcomas are associated with a fusion gene protein from chromosomal translocation. In other words, a molecular event leads to exchange of DNA between two chromosomes. As a consequence of that

exchange, a new fusion gene is created, which is pathogenic for the malignancy. Researchers have been aware of the existence of this fusion gene for Ewing sarcoma and synovial sarcoma for over 20 years, and we have been able to categorize almost all the sarcomas with this feature.

It has long been believed that although chromosomal translocation is a common event in sarcomas and leukemia (eg, chronic myelogenous leukemia [CML]), it is rare in epithelial cancers. Dr. Arul Chinnaiyan from the University of Michigan has discovered fusion proteins in prostate cancer. This discovery resulted from remarkable developments in gene-expression profiling. Now, fusion proteins are known to be occurring in a common epithelial cancer. Not only are these fusion proteins responsible for the development of the pathogenesis of the cancer, they are also extraordinary targets. Theoretically, if the fusion protein could be inhibited, the cancer should be cured. There are ongoing efforts in drug development to investigate the role of fusion proteins in sarcoma development. If this approach is successful, Dr. Chinnaiyan and his colleagues will be interested in developing small molecules against the fusion proteins responsible for prostate cancer. There is now a strong link in terms of drug development between sarcomas and this far more common epithelial cancer.

H&O What is some of the ongoing research in this setting with the use of tyrosine kinase inhibitors?

LB The sarcoma field played a key role in the development of imatinib (Gleevec, Novartis), a tyrosine kinase inhibitor. One of its indications is in the treatment of gastrointestinal stromal tumors (GIST). Furthermore, one of the indications of the multitargeted tyrosine kinase inhibitor sunitinib (Sutent, Pfizer) is in the treatment of refractory GIST. Sarcoma investigators have played a pivotal role in the development of drugs targeted against tyrosine kinase that are widely used in more common cancers like CML or renal cell carcinoma.

Many of the newer tyrosine kinase inhibitors also are antiangiogenic. Whether or not angiogenesis is an important target in sarcoma is unknown. It is known that inhibition of vascular endothelial growth factor (VEGF) is not important in GIST. One hypothesis for sunitinib's advantage over imatinib in refractory GIST was not only its inhibition of *Kit* and platelet-derived growth factor receptor (PDGFR), but also VEGF. This hypothesis is now rejected; instead, a mutation of *Kit* or PDGFR is relevant to sunitinib's efficacy when tumors become refractory to imatinib. It is easy to fall into the trap of thinking that inhibition of angiogenesis must be important to treating cancers.

Dasatinib (Sprycel, Bristol-Myers Squibb), an inhibitor of *Src*, is approved for the treatment of refractory

CML, and it is being studied by the Sarcoma Alliance for Research through Collaboration group. Dasatinib has potential to be important in the treatment of sarcomas, particularly those that originate in bone. Another multitargeted tyrosine kinase inhibitor AZD0530 is a more potent inhibitor of *Src* and will soon be under investigation in pulmonary metastatic osteosarcoma.

H&O What is the status of the inhibition of insulin-like growth factor receptor in patients with sarcoma?

LB Discussions of inhibition of insulin-like growth factor receptor (IGFR) pathway have recently exploded in the literature. At least 11 antibodies and six small molecules targeted against IGFR are in development by pharmaceutical companies. The practical difficulty of developing 17 molecules at the same time is an important concern, raising significant societal and scientific questions about priorities. Nonetheless, the existence of so many potential agents is great evidence that IGFR must be an important target. The ligands IGF-1 and IGF-2 as well as the IGF binding proteins are described to be important in a host of cancers, including prostate, colon, breast, and lung cancer. Furthermore, there is an extensive amount of preclinical and phase I clinical data showing that IGFR inhibition leads to clinical benefit in Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma. This is a field of intense study.

H&O What have been the findings with treatments targeting oncogenes?

LB Researchers have not yet successfully exploited *p53*, mouse double minute 2 (*MDM2*), or multidrug resistance (*MDR*), but these are all interesting genes that are relevant to sarcoma. The *Met* gene is also very important to sarcoma, as has been understood preclinically to be important for years. There are *Met* inhibitors in development that may well become important. New molecules targeted against PI3kinase and *ATK* are in clinical study. Has the role of *p53*, which is pivotal in the development of sarcoma, been translated into a therapeutic success? The answer is no. Has the importance of *MDR* and *MDM2* in native or secondary resistance to drugs in sarcoma been translated into a therapeutic success? No. However, all these targets hold great promise for future sarcoma patients.

H&O What is the status of inhibition of mammalian target of rapamycin in sarcoma?

LB There are three inhibitors of mammalian target of rapamycin (mTOR) in various stages of clinical development: temsirolimus (Torisel, Wyeth) has been approved

by the FDA for the treatment of renal cell carcinoma; RAD001 (Novartis) is expected to be approved in the coming year; and deferolimus (Ariad) has been researched in a phase II study in patients with sarcomas. Whether these drugs are substantially different from each other clinically has yet to be elucidated.

For that matter, whether any of these analogs are superior to the parent rapamycin has yet to be demonstrated at any level. Indeed, Schuetze and Maki reported on clinical benefit of rapamycin in far advanced sarcoma patients. There are dual inhibitors of the mTOR pathway under preclinical development that may be more important clinically than the current inhibitors. mTOR is unquestionably an important pathway in sarcomas, as it is in renal cancer. The value of these drugs in sarcoma, however, is questionable. The final results of the phase II study of AP23573 are not yet available, but there have been preliminary clinical benefits reported in abstracts, including a few partial remissions and disease stabilization (which is difficult to interpret in a phase II study). Temsirolimus was regarded as negative in sarcoma by Wyeth, but our interpretation found the same level of stabilization that as has been preliminarily seen with AP23573 was seen with temsirolimus. The temsirolimus phase II study in sarcoma was reported as negative, as disease stabilization was not an endpoint. There are now plans to study the parent, rapamycin, in sarcoma patients in a collaborative study of the Universities of Chicago and Michigan. The extraordinary interaction of IGFR inhibition and mTOR inhibition elicits great excitement among researchers investigating treatments for sarcoma and other cancers. There is a great deal of interest in using this combination for the treatment of breast, colon, and prostate cancer.

H&O What advances have been made with cytotoxic chemotherapy in this setting?

LB Ecteinascidin-743 (also known as trabectedin) was approved by the European Medicines Agency because of its significant activity in myxoid liposarcoma, leiomyosarcoma, and synovial sarcoma, among others. The drug has not been registered for approval by the FDA, which denies patients with sarcoma in the United States the opportunity to receive this effective drug. The reason this drug has not been developed further in the United States could be that the sarcoma market is not large enough, which, if true, would be shameful. Another important development was the randomized trial of the combination of gemcitabine (Gemzar, Eli Lilly) and docetaxel (Taxotere, Sanofi-Aventis) versus gemcitabine alone, a monotherapy thought to be active in refractory sarcoma patients. The doublet was found to be more effective than gemcitabine alone in all

sarcoma subtypes in response and overall and progression-free survival. As such, it is erroneous to think that progress is only to be made with tyrosine kinase inhibitors.

Additionally, there are several other exciting avenues of research at various stages of development. For example, there are ifosfamide-like compounds under development that seem to have demonstrated clinical activity with seemingly less toxicity than the parent drug. The potential importance of heat-shock protein inhibition, particularly heat-shock 90, seems to have particular relevance in refractory GIST. This target offers a very different way of treating cancer.

There has been a great deal of research on how, when cancer metastasizes to bone, the metastatic cell establishes itself in that environment. Metastatic cancer to bone is a devastating event that causes enormous morbidity in women with breast cancer and men with prostate cancer. Promising research in the field of sarcoma and metastatic bone cancer concerns the immunologic response to cancer cells in the bony matrix. There is an immunologic stimulant MTPPE, which is a derivative of *Cryptosporidium parvum* studied by the Children's Oncology Group and seemed to confer a significant survival advantage in the setting of adjuvant osteosarcoma. As such, there has been a renaissance in interest in immunologic approaches to sarcoma. The Karolinska Institute has promoted the therapeutic benefit of interferon in osteosarcoma for 25 years or so. The current European and American collaboration in osteosarcoma is studying interferon in a prospective randomized trial.

Suggested Readings

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