

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Treatments for Sarcoma

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H&O What is the history behind the current standard of care for sarcoma?

IJ For many years, the only chemotherapy available for sarcoma was the combination of doxorubicin and ifosfamide, or more commonly in Europe, single-agent doxorubicin, as clinical trials have failed to demonstrate any progression-free survival or overall survival advantage for combination therapy. In the late 1990s, things started to change with the advent of imatinib (Gleevec, Novartis) for the treatment of gastrointestinal stromal tumor (GIST), which revolutionized the management of that disease. Currently, we are able to treat effectively 80–90% of patients with unresectable or metastatic GIST using imatinib and newer drugs such as sunitinib (Sutent, Pfizer). This discovery set the scene for a major refocus of clinical research in sarcomas, which until then has been regarded as too to be of interest to the pharmaceutical industry.

H&O What agents are currently being investigated in sarcoma?

IJ To date, GIST has been the area with the most research and the agents with the most efficacy in GIST are small molecule tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib (Sprycel, Bristol-Myers Squibb), masatinib, sorafenib (Nexavar, Bayer), and nilotinib (Tasigna, Novartis). The major success of imatinib demonstrated the ability to target sarcomas with TKIs, and hence, a number of other subtypes of sarcoma have become, to a certain extent, treatable. TKIs have been used principally

for their anti-angiogenic properties, such as inhibitors of VEGFR like pazopanib (Votrient, GlaxoSmithKline), which showed activity against leiomyosarcoma, synovial sarcoma and other sarcomas including those of vascular origin. Sorafenib and sunitinib have also demonstrated some activity in sarcoma and have been examined anecdotally or in small phase II studies.

Pazopanib is being investigated in a large randomized placebo-controlled phase III study, which has recently completed accrual and has survival as its endpoint. The study has been expanded in order to ensure that enough events will be observed to determine whether angiogenesis inhibition can prolong survival in patients with chemotherapy-refractory advanced sarcoma.

Nilotinib is another agent that is being evaluated in GIST. It has demonstrated activity in tumors progressing on imatinib, and appears to have some utility after failure with imatinib and sunitinib. Nilotinib is also being examined in the first-line setting, as it is a stronger binder to the ATP binding pocket of mutant activated KIT, which is the mutant receptor that drives the majority of GIST. At present, nilotinib is not licensed for any of these indications.

H&O What role does a patient's mutational status play in selecting treatment?

IJ We now look at the mutational status of most patients with advanced GIST from the outset, and have recognized one situation where sunitinib may be superior to imatinib and that is when there are no detectable mutations (wild-type disease). In patients with the exon 9 mutation

in KIT, higher doses of imatinib or sunitinib are more effective than standard doses of imatinib. However, there is a mutation in PDGF alpha receptor called the D842V mutation (PDGFRA-D842V), which is unresponsive to imatinib, sunitinib, and most other TKIs, and in patients harboring this mutation, we do not have a good therapeutic option. There is some evidence that dasatinib may be effective, but it has not been rigorously tested in this setting.

In regard to second-line treatment, the most common mechanism leading to resistance is the development of second mutations, which change the binding pocket or change the configuration of the receptor. Those mutations that occur in the ATP binding pocket in exons 13 and 14, which confer resistance to imatinib, are responsive to sunitinib. However, those that change the activation loop in exons 17 and 18 of KIT do not respond to sunitinib, and thus other drugs are required. At the moment, it is not clear what other drugs should be used or whether there is activity with sorafenib. Activity has been observed with dasatinib in refractory disease; however, data with masatinib are not as clear—responses have been seen, and in previously untreated patients, activity appears to be at least comparable if not superior to that with imatinib.

Generally, prior to study enrollment, the primary tumor characteristics define response. The issue with secondary mutations in GIST is that it is possible to get multiple mutations in the same patient, even in the same tumor. Therefore, just sampling in 1 or 2 areas might not provide the whole picture of what mutations are driving resistance, and has therefore been of limited value. Increasingly, we are defining the patient population using molecular pathology tools such as the presence of a translocation to confirm, for example, a diagnosis of myxoid liposarcoma.

What is frustrating thus far is that we have not obtained many examples in which knowing the translocation gives us information on how to treat the tumor, as there are many translocation partners or genes that are affected by that transcription factor and defining what the key target can be difficult. In fact, we have known about the exon 18 translocation on synovial sarcoma for approximately 20 years, but it has not told us how to treat the disease with a molecularly targeted agent.

H&O In what other types of sarcomas are new agents being investigated?

IJ Other type of diseases in which TKIs have shown some interest include an extremely rare tumor called alveolar soft part sarcoma of which there are only approximately 12–15 cases a year in the United Kingdom. Patients with this diagnosis live for a long time, even in metastatic stage,

so the prevalence can be relatively high considering its rarity. This disease does not respond to chemotherapy but does respond to anti-angiogenesis inhibitors; activity has been reported with sunitinib and cediranib (Recentin, AstraZeneca). We reported a small series of patients at The Connective Tissue Oncology Society meeting in 2008 and updated it last year with data that showed durable prolonged responses for 2 years or more in the lungs and in the brain. A phase II trial with cediranib in patients with alveolar soft part sarcoma is underway at the National Cancer Institute Children's Branch and we are hoping to conduct a randomized study in Europe.

MET inhibitors also appear promising in alveolar soft part sarcoma, and a response has been reported in clear cell sarcoma, which has been completely unresponsive to standard conventional chemotherapeutic agents such as doxorubicin.

Another type of sarcoma is dermatofibrosarcoma protuberans, a rare skin tumor, which is also treated with imatinib, as it is driven by a translocation that upregulates platelet derived growth factor beta (PDGFB). Inhibition of the PDGF receptor by imatinib can be effective in patients with unresectable disease or disease that has transformed into fibrosarcoma.

ALK is target that may be of interest in inflammatory myelofibroblastic tumors, where that particular target is upregulated because of the particular genetic change in the tumor cell.

Theoretically, targeting p53 dysregulation might be effective in dedifferentiated liposarcoma where there is an amplification that causes upregulation of MDM2, which inhibits p53 and also co-amplification of CDK4. This produces a concurrent inhibition of apoptosis and a drive to proliferation. If it is possible to reactivate the apoptotic mechanism, perhaps with BCL2 inhibitors, it may be a viable target in dedifferentiated liposarcoma where again chemotherapy is not very effective.

Trabectedin (Yondelis, Zeltia/J&J) is active in leiomyosarcoma and liposarcoma, particularly in myxoid liposarcoma. Apart from this, the disease that has been the most responsive to chemotherapy is leiomyosarcoma of the uterus, where we have seen durable responses. Other sarcoma types that are less well studied such as synovial sarcoma are also sensitive to trabectedin. The overall data show that the percentage of patients who had objective remission was relatively small (8–10%), but approximately 30% of patients have minor responses and prolonged stable disease with relief of symptoms. Certain liposarcomas, particularly the well differentiated and dedifferentiated types mainly arising in the abdomen are not very responsive to chemotherapy. Trabectedin is a tetrahydroisoquinoline alkaloid isolated from the marine tunicate *Ecteinascidia turbinata*. It is a drug that now

used regularly in Europe since it was licensed in 2007 and was very recently approved by the National Institute for Health and Clinical Excellence in the United Kingdom. However, as yet it has not been approved or the US Food and Drug Administration in the United States.

In phase I trials, we have also seen some hints of activity with histone deacetylase inhibitors in sarcoma patients. There is a range of new targets, including mammalian target of rapamycin (mTOR) inhibitors, particularly small molecule TOK1 and TOK2 inhibitors, that should be tested, because there is evidence of upregulation of the mTOR pathway in chondrosarcoma and chordoma. It is likely to be involved in quite a number of sarcomas where the PI3 kinase pathway is known to be active.

One of the challenges is that there are so many new drugs and targets being developed that it becomes a case of what to focus on and how to best enrich the target population for those tumors that are more likely to benefit. We are now beginning to see clinical trials with a much tighter focus on specific sarcoma subtypes.

H&O What other treatment approaches aside from chemotherapy are employed in sarcoma patients?

IJ All patients who have resectable tumors undergo surgery and, commonly, radiotherapy, as well as standard adjuvant therapy. All patients with high-grade tumors are likely to receive adjuvant radiotherapy. In patients who develop metastatic disease, local therapies are of limited use and radiofrequency ablation and surgery are procedures that are frequently performed for liver and lung

metastases. In fact, metastasectomy plays a key role in the management of some sarcomas, particularly osteosarcoma. It is not clear whether radiotherapy is going to extend its use because of technical developments, but it is likely that in some advance cases, technologic development will enable essentially local therapies to be applied to distant metastatic disease.

Immunotherapy has also been looked at in sarcoma. We see various diseases where there is a translocation that produces a unique fusion protein, which should not be present in any other solid body, and thus we would expect a vaccine against that fusion protein to be effective, but this far it is not. Synovial sarcoma has been the archetype for sarcoma vaccine studies, and a number of vaccines have been developed against the fusion protein. Unfortunately, it has not been possible to demonstrate a true meaningful immune response that actually causes tumor cell kill.

Another type of targeted therapy is a naturally occurring virus, the reovirus, which is cytotoxic to cells that are driven by mutant RAS or overexpressed RAS, and many cancer cells are therefore susceptible to it. Phase II studies in sarcoma patients have showed some intriguing hints of activity with reovirus in terms of disease stabilization.

Suggested Readings

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