New Strategies in Sarcoma Therapy: Linking Biology and Novel Agents

Katherine A. Janeway and Robert G. Maki

Abstract

The ability to better interrogate the genetic state of a given cancer is giving rise to a new paradigm in cancer therapeutics in which the specific genetic alterations that give rise to the cancer inform the therapeutic decision-making for that specific patient. Sarcomas of soft tissue and bone represent model diseases that underscore this paradigm. However, many barriers prevent linkage of one of the 75 or more different types of sarcoma to novel therapeutic agents. In the present perspective, the authors outline key therapeutic opportunities and hurdles in clinical sarcoma research, focusing on specific examples of sarcomas that are on the verge of new breakthroughs, as well as those in which promise has not lived up to expectations. Focused clinical trial design, ideally with several biomarker or histology-specific arms, is one means to be simultaneously parsimonious and inclusive. Clin Cancer Res; 18(21): 5837–44. ©2012 AACR.

Background

Sarcomas represent a family of rare cancers of bone and soft tissue accounting for less than 1% of cancer in adults and approximately 15% of pediatric cancer (1). They are biologically heterogeneous, with more than 50 histologic subtypes identified in soft tissue and more than 20 in bone, in keeping with the multiple types of connective tissue that comprise the scaffolding of the human body (2).

Given their heterogeneity, a number of approaches have been used to characterize them, including histology (e.g., the 3 classes of liposarcoma), genetics (aneuploid sarcomas vs. those with driver mutations or specific chromosomal translocations), anatomic primary site, or whether they are more prevalent in children or adults. In general, while children who get sarcomas will most typically receive multimodality therapy with surgery, chemotherapy, and radiation, in adults, the use of chemotherapy in the primary disease setting is not as widespread, given the more limited benefit observed with the use of adjuvant systemic therapy in many subtypes (3).

The biology of sarcomas is interesting due to the involvement of particular signaling pathways in specific sarcoma subtypes (4, 5), many of which have parallels in other cancers (Fig. 1). The most common sarcomas that arise in children are aneuploid sarcomas, such as osteogenic sarcoma as well as those with specific translocations, such as Ewing sarcoma and alveolar rhabdomyosarcoma (ARMS). In adults, the most common sarcomas are usually aneuploid, including leiomyosarcoma, and undifferentiated pleomorphic sarcoma (UPS, formerly termed MFH, malignant fibrous histiocytoma), whereas other sarcomas that have specific genetic changes, such as KIT mutation in gastrointestinal stromal tumor (GIST) or the SS18-SSX translocations seen in synovial sarcoma, are collectively somewhat less common.

In this commentary, we highlight the hurdles that face clinical investigations into sarcomas more common in children and adults, as well as new therapeutic options, some of which have been decades in the making. Tantalizing recent discoveries place us on the cusp of a new era linking tumor genetics to specific therapeutics for at least a few of the histologies discussed herein, but the ballast otherwise hindering more rapid clinical research may prove difficult to jettison.

Sarcomas more common in children

The most common histologies of sarcoma treated in children include osteogenic sarcoma, Ewing sarcoma, rhabdomyosarcoma (alveolar and embryonal subtypes, primarily), and less commonly other sarcomas, such as synovial sarcoma and desmoplastic small round cell tumor, which as a group are termed nonrhabdomyosarcoma soft tissue sarcomas. New therapeutics stand to impact upon the way we treat each of the most common childhood sarcoma diagnoses (Table 1).

Osteosarcoma. Outcomes for newly diagnosed patients with osteosarcoma had not changed in over 20 years (6). The lack of progress reflects the dearth of effective newer agents, save for the immunotherapeutic milamudride, which is now approved outside the United States and...
The challenge in identifying new agents with activity in osteosarcoma is a function of the complex biology of this disease, challenges in detecting radiographic responses in tumors with calcified stroma and deficiencies in risk stratification. While there have been no research discoveries pointing to a single essential pathway in osteosarcoma, preclinical studies have identified new agents with potential clinical activity.

Two agents of significant interest are antidisialoganglioside (GD2) antibody and receptor activator of NF-κB (ligand; RANKL) antibody denosumab. GD2 is a cell surface sialic acid–containing glycosphingolipid expressed normally in central nervous system, peripheral nerves, and melanocytes. In neuroblastoma anti-GD2 antibody, Ch14.18 significantly improves event free and overall survival (7). More than 90% of osteosarcomas express GD2 (8). In the phase I/II trial of the murine anti-GD2 antibody, 14.2G2a, plus IL-2, 1 of 2 patients with osteosarcoma treated had a complete response persisting for 8 months (9).

RANKL and its receptor RANK are members of the tumor necrosis factor family of receptors and ligands with the physiologic function of regulating bone turnover. Osteosarcoma expresses both RANK and RANKL and in osteosarcoma, RANK–RANKL interaction activates downstream signaling and modulates gene expression (10, 11). Interfering with RANK–RANKL interaction in vivo decreases osteosarcoma growth and metastatic tumor burden (12–14). These data will hopefully build on a clinical trial in giant cell tumor of bone (GCTB), in which interruption of RANKL signaling by virtue of denosumab led to rapid and sustained radiological changes with clinical benefit (pain relief) in patients with recurrent or metastatic GCTB (15).

**Ewing sarcoma.** Ewing sarcoma is a small round blue cell tumor that arises from bone or soft tissue and is characterized by a translocation involving EWSR1 and one of several genes in the E twenty-six family of transcription factors, most often FLI1. The EWSR1-FLI1 translocation is referenced later. The challenge in identifying new agents with activity in osteosarcoma is a function of the complex biology of this disease, challenges in detecting radiographic responses in tumors with calcified stroma and deficiencies in risk stratification. While there have been no research discoveries pointing to a single essential pathway in osteosarcoma, preclinical studies have identified new agents with potential clinical activity.

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present in 85% of Ewing sarcoma. The insulin-like growth factor (IGF) pathway has been shown to be important in Ewing sarcoma. High expression of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 1 receptor (IGF1R) is seen in Ewing sarcoma. The EWS-FLI1 translocation is associated with decreased IGFBP-3 expression, resulting in decreased IGF1R signaling.

Inhibiting the IGF pathway decreases Ewing sarcoma proliferation both in vitro and in vivo (16). In a phase II study of 106 patients with recurrent or refractory Ewing sarcoma, anti-IGF1R antibody figitumumab produced a 14% response rate (17). In a phase II study of R1507, a different IGF1R monoclonal antibody, 115 patients were enrolled and the response rate was 10% (18). The low response rates exemplify the need to identify a biomarker that is associated with disease responsiveness and to examine the signaling feedback loops that may promote resistance. There is a great interest in further studying the activity of IGF1R antibodies in Ewing sarcoma, highlighted by the success of the R1507 trial to bring together pediatric oncologists and medical oncologists on one common study, something that has been difficult to achieve in practice. However, planning additional IGF1R inhibitor–based trials will be challenging, because many pharmaceutical companies canceled their IGF1R antibody programs when trials in carcinomas failed to show activity (19).

In 2012, 2 articles highlighted the possible use of PARP inhibitors in Ewing sarcoma (20, 21), recalling a basic science finding from more than a decade earlier (22). While a phase III trial has been completed in breast cancer, PARP inhibitors have not been systematically examined in sarcomas. To begin to remedy this deficiency, a phase II trial of olaparib in patients with relapsed and recurrent Ewing sarcoma is enrolling patients (23), and further clinical trials are anticipated.

**Rhabdomyosarcoma.** Rhabdomyosarcomas are malignancies of skeletal muscle most commonly affecting children under age of 5 years but also occurring in adolescents and young adults. There are 2 major histologic subtypes, alveolar and embryonal. ARMS is characterized by translocations between the DNA-binding domain of either PAX3 or PAX7 and the transactivation domain of FOXO1. ARMS has a poorer prognosis and more commonly occurs in older children, adolescents, and young adults. As is seen in Ewing sarcoma, preclinical and clinical data implicated IGF signaling as essential in rhabdomyosarcoma. Both alveolar and embryonal rhabdomyosarcoma (ERMS) have high expression of IGF-II and IGF1R through diverse mechanisms. Loss of imprinting at IGF2 locus is present in Ewing sarcoma, preclinical and clinical data implicated IGF signaling as essential in rhabdomyosarcoma. Both alveolar and embryonal rhabdomyosarcoma (ERMS) have high expression of IGF-II and IGF1R through diverse mechanisms. Loss of imprinting at IGF2 locus is present in Ewing sarcoma. The fusion transcription factor PAX3-FOXO1 targets the IGF1R promoter (24). A phase II trial evaluating the feasibility of adding cixutumumab, an IGF1R antibody, with or without temsirolimus, to intensive chemotherapy is underway (24).

**Inflammatory myofibroblastic tumor.** Inflammatory myofibroblastic tumor (IMT) is a rare, locally aggressive tumor. It is biologically heterogeneous but was found to harbor translocations involving ALK in 50% of patients, particularly younger patients (25, 26). Crizotinib is a small-molecule inhibitor of anaplastic lymphoma kinase (ALK). In ALK-translocation positive non–small cell lung cancer, crizotinib has substantial activity and is being evaluated in phase III trials. In the case of non–small cell lung cancer, even though only 5% have ALK mutations the total number of patients per year in the United States with non–small cell lung cancer is 7,500, making a number sufficient for randomized studies. Conversely, IMT affects perhaps 50 patients in the United States annually, a number too small to examine in randomized trials. Nonetheless, activity of crizotinib was shown by allowing patients with IMT to be accrued to phase I studies in adults (27), and children (28, 29).

**Sarcomas more common in adults**

**Scope of the problem.** Sarcomas are more uncommon in adults relative to other cancers, and are more heterogeneous. Sarcoma subtypes are in part a function of anatomic primary site and patient age. These data alone can direct one to a specific differential diagnosis. GIST, UPS, leiomyosarcoma, and the 3 forms of liposarcoma are the most common subtypes in adults, although versions of sarcomas more common in children are also seen, with interesting...
clinical variations. For example, Ewing sarcoma is much more common in soft tissue in adults than in bone, the most common site in children, and rhabdomyosarcoma is far more commonly the pleomorphic subtype than in children, in which embryonal and alveolar subtypes predominate.

Despite their heterogeneity, over the last several years a variety of novel agents have been found to be active in specific sarcoma subtypes. These are outlined in Table 2; some are described in greater detail later. The same issues with respect to pediatric sarcomas apply, although for some more common sarcomas there are sufficient numbers of patients to complete randomized clinical trials.

Gastrointestinal stromal tumor. GIST remains the best example of a sarcoma in which the use of a kinase-directed agent led to impressive clinical results (30). This topic is well addressed elsewhere, although notably for the first time a survival advantage was shown for use of imatinib in the adjuvant setting (31). Patients who received 3 years of imatinib had improved 5-year survival as compared with patients who received only 1 year of therapy. It will be interesting to see if there is any relationship between genotype and outcome, not thoroughly discussed in the initial manuscript, which will further help define who may best benefit from longer courses of imatinib.

An interesting metabolic pathway genetic alteration can lead to a form of GIST that occurs predominantly in children and young adults. In this "SDH-negative" form of GIST, loss of succinate dehydrogenase (SDH) expression is observed, and may ultimately provide new means to treat both these so-called "pediatric," syndromic GISTs, and much more common KIT or PDGFRA mutant GIST (32, 33). Lisitinib will undergo evaluation for SDH-negative GISTs; in a similar way, crenalonib is being studied in the relatively rare D842V PDGFR A mutant GIST.

Synovial sarcoma. Synovial sarcoma has been under close study to understand how its SS18-SSX translocation product drives the phenotype of this cancer. The cell of origin, hitherto unknown, was suggested to be the satellite cell of skeletal muscle, based on the context-dependent tumor growth seen when the same transgene was introduced into different cell types (34). Work by Ladanyi and colleagues highlighted how monophasic and biphasic varieties of the cancer develop based on the SS18-SSX subtype (35).

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent(s)</th>
<th>Sarcoma subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity shown in clinical trials or case series</td>
<td>KIT, PDGFR</td>
<td>Imatinib, sunitinib, sorafenib, regorafenib, dasatinib</td>
</tr>
<tr>
<td>Autocrine signaling loop(?)</td>
<td>PDGF, CSF1</td>
<td>Imatinib</td>
</tr>
<tr>
<td>RANK–RANKL</td>
<td>Denosumab</td>
<td>Angiosarcoma, solitary fibrous tumor/ hemangiopericytoma, alveolar soft part sarcoma, clear cell sarcoma</td>
</tr>
<tr>
<td>VEGF and/or VEGFR</td>
<td>Bevacizumab, sorafenib, sunitinib, pazopanib, cediranib, others</td>
<td>Ewing sarcoma, desmoplastic small round cell tumor</td>
</tr>
<tr>
<td>IGF1R</td>
<td>IGF1R monoclonal antibodies</td>
<td>Wiscott–Aldrich syndrome, osteosarcoma</td>
</tr>
<tr>
<td>ER</td>
<td>Tamoxifen</td>
<td>Endometrial stromal sarcoma</td>
</tr>
<tr>
<td>mTOR (TORC1)</td>
<td>Sirolimus, other TOR inhibitors</td>
<td>Perivascular epithelial cell tumor family (PEComa)</td>
</tr>
<tr>
<td>ALK</td>
<td>Crizotinib</td>
<td>IMT</td>
</tr>
<tr>
<td>HDM2</td>
<td>RG7112</td>
<td>Myxoid-round cell liposarcoma</td>
</tr>
<tr>
<td>CDK4</td>
<td>PD0332991</td>
<td>WD–DD LS</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>Autologous NY-ESO-1 T cells</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Activity suggested in individual case reports or translational science articles</td>
<td>EGF family</td>
<td>Gefitinib, cetuximab</td>
</tr>
<tr>
<td>(Histone) deacetylase</td>
<td>Vorinostat</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>26S Proteasome</td>
<td>Bortezomib</td>
<td>GIST</td>
</tr>
</tbody>
</table>

Table 2. Status of newer agents in different sarcoma subtypes

Abbreviations: CSF1, colony stimulating factor 1; EGF, EGF receptor; ER, estrogen receptor; PDGFR, platelet-derived growth factor (receptors); TORC1, (mammalian) target of rapamycin complex 1.
After several years of work leading to the demonstration that hsp90 inhibitors and histone deacetylase (HDAC) inhibitors could be a useful option for this sarcoma subtype (36–39), Nielsen and colleagues began to decipher the mechanism of this approach in a publication on the biochemistry of the SYT-SSX protein and how it links transcription factors ATF2 and TLE1 (40). Gene knockdown or an HDAC inhibitor decreases synovial sarcoma growth and causes apoptosis. These studies provide an obvious inroad to clinical trials using HDAC inhibitors in synovial sarcoma. The relative lack of overlapping toxicity of HDAC inhibitors with cytotoxic agents or kinase-directed agents may allow for their combination. Such combination studies are underway, although as noted earlier none are presently sarcoma-specific.

Well differentiated-dedifferentiated liposarcoma. A different angle on deacetylase inhibitors, as well as other novel-targeted agents, arises in a discussion of well differentiated–dedifferentiated liposarcoma (WD–DD LS), one of the most common forms of sarcoma. WD–DD LS is a frustrating diagnosis that often occurs in the abdomen/retroperitoneum and recurs again and again, with deaths typically from local disease progression rather than overt metastases. A careful analysis from Taylor and colleagues identified 8% of DD LS with mutations in HACD1 (41), suggesting there will be other epigenetic mechanisms by which WD–DD LS requires to survive with what are hundreds or thousands of copies of the same sequencing encoding HDM2, CDK4, and neighboring genes on chromosome 12q (5).

These data underscore the well-recognized amplification of chromosome 12q, the mechanism of which is still somewhat mysterious (42). This characteristic amplification brings into focus the use of human homologue of murine double minute 2 (HDM2) or cyclin-dependent kinase 4 (CDK4) inhibitors in this form of liposarcoma (43). Phase I–II data have been collected for patients with WD–DD LS treated with HDM2 inhibitor RG7112 before surgery, and CDK4 inhibitor PD0332991 has at least minor activity in phase I of WD–DD LS in a recent clinical trial (44). While no agent has yielded the dramatic results shown with kinase-directed therapeutics in GIST, these agents represent measurable advances upon which future investigations can build.

Challenges and opportunities in identifying novel agents for sarcomas

A number of challenges face clinical investigators interested in studying novel agents in sarcomas. One such challenge is access to new agents. In the case of IGF1R antibodies, academic researchers and cooperative groups were interested in designing further trials of IGF1R antibodies in Ewing sarcoma, but many pharmaceutical companies ceased developing IGF1R antibodies because of disappointing trial results in carcinoma. Furthermore, complicating access to drugs for clinical trials in sarcomas is the issue of early phase trials of novel agents in pediatric patients. The initial phase II trial of PARP inhibitors in Ewing sarcoma will be conducted in adults because none of the PARP inhibitors have yet been studied in phase I in children, preventing an inclusive trial with children and adults until the appropriate pediatric phase I has been conducted.

Because most sarcomas in children are treated with multi-modality therapy including chemotherapy, an additional challenge is faced after a novel agent has been shown to have single-agent efficacy in sarcoma. To be used in newly diagnosed patients, the novel agent must be integrated with existing therapy, which may produce unanticipated toxicity. This difficulty has been addressed with at least 2 approaches, including studying combinations in poor prognostic populations, or studying the agent in a maintenance fashion. The Children’s Oncology Group (COG) study ARST08P1 will combine cixutumumab or temozolomide or both in patients with high-risk rhabdomyosarcoma, looking at toxicity to see if it will be possible to incorporate either agent in the next phase III study in rhabdomyosarcoma (45).

Like many sarcomas, IMT also highlights a third issue common with pediatric and adult sarcomas, specifically the lack of an appropriate model system to serve as a surrogate for patients. Preclinical data are helpful, even essential, to spur clinical trials, as has happened in pediatric and adult sarcomas alike. In an effective model system, there is also ideally a biomarker of drug activity that can be used in the disease of interest. With lack of an effective model, we are reduced to paraffin tumor samples or frozen tissue, from which limited data can be gleaned. Fortunately, a number of models of sarcomas have been developed in recent years (34, 46, 47) and are currently being used for preclinical research.

Key elements of trial design, such as biomarker-driven studies, and the collaboration of investigators between centers or between disciplines, for example, pediatric and medical oncology, are equally important in linking a diagnosis with a new therapeutic. The COG is the only National Cancer Institute (NCI)–funded pediatric cancer cooperative group; COG and its predecessors have served as the conduit for a number of phase I–II–III cancer clinical trials in sarcoma (24) and routinely permits adult patients with appropriate diagnoses to participate in its studies. Sarcoma Alliance for Research through Collaboration’s study of IGF1R antibody R1507 enrolled both children and adults, and is a good example of cooperation between pediatric and adult oncologists (18). Another example of cooperation between pediatric and medical oncologists in preclinical research is the identification and characterization of SDH-deficient GIST. Finally, the use of a biomarker to identify patients for priority enrollment on early-phase trials allowed the study of crizotinib in children with IMT (29).

On the Horizon

The most common sarcomas, aneuploid tumors in adults more than 50 years of age, have shown little responsiveness to kinase-directed agents studied in the past decade, and
have proved frustrating in the era of kinase-directed therapy and GIST, although there is equal frustration for a variety of translocation-associated sarcomas as well (Table 3).

There are glimmers of hope that aneuploid sarcomas will respond to newer generations of agents, such as some of the otherwise chemotherapy refractory refractory diagnoses that are shown to respond to kinase inhibitors. Osteosarcoma therapy has been changed, at least in Europe, with the demonstration of the activity if mifurtmatide in a phase III clinical trial (48, 49), work that was propelled by translational research (50). A fraction of osteosarcomas respond to multi-targeted tyrosine kinase inhibitors (51). Furthermore, pazopanib was approved in 2012 for use in patients with soft tissue sarcomas other than GIST or liposarcoma that are refractory to other systemic therapeutics (52). While the mechanism of action of pazopanib in sarcomas in general is unknown, VEGF receptor (VEGFR) blockade may be important for the observed responses of alveolar soft part sarcoma and clear cell sarcoma to sunitinib and of alveolar soft part sarcoma to cedirabip (53, 54; Table 2), which may be a general phenomenon for VEGFR inhibitors as with renal cell carcinoma. Finally, leiomyosarcomas have upregulation of kinases and markers of inflammation that may lead to less toxic therapeutic options (55).

A prescription for efficient sarcoma clinical trials
Small studies of 10 to 20 patients with a specific diagnosis can rule in or rule out substantial activity (e.g., a 30% RECIST response rate) of a new drug. At the same time, small histology or biomarker-specific studies are unattractive to Institutional Review Boards and clinical trials offices that look to accrual as a metric for keeping a study open. As a result, a design incorporating multiple histologies is preferred over several independent small studies. The choice of clinical trial design is important, given what proved to be a large number of patients treated with an ineffective agent in one randomized discontinuation phase II study in a group of unselected sarcomas (56) and remains an active topic of discussion.

Ideally, studies will be conducted with pre- and posttreatment biopsies to gain the maximum data form the smallest number of patients, which can ethically only be done in adult patients, if at all. A less invasive approach employs correlative radiological studies, such as 2[18F]fluoro-2-deoxy-o-glucose (FDG)- or fluoro-o-thymidine–positron emission tomography (FLT-PET) as part of the conduct of these clinical trials, which has proved a useful approach in assessing the response to therapy in studies of cytotoxic and kinase-directed agents alike (57, 58). Small steps do add up, and this incremental approach, driven by careful drug/histology selections on the basis of biology, will hopefully lead to greater progress in this rare and diverse group of cancers.

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Conception and design: K.A. Janeway, R.G. Maki
Writing, review, and/or revision of the manuscript: K.A. Janeway, R.G. Maki
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.G. Maki

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Table 3. A "most wanted" list of sarcoma diagnoses in need of new agents

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reference</th>
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Clinical Cancer Research

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