Abstract

Sarcomas represent a heterogeneous group of tumors that are composed of a wide range of tumor types with different natural histories and therapeutic approaches. Recent discoveries have identified specific molecular alterations in the pathogenesis of many of these tumors. These specific molecular alterations acquired during sarcomagenesis lead to the phenotypic changes of malignancy, namely proliferation, survival, invasion, metastasis, and angiogenesis. Inhibition of these molecular alterations by targeted therapy represents an opportunity to reverse the biologic basis of tumor formation in soft tissue sarcomas (STSs) and bone tumors (BTs). In this chapter we discuss a general overview of sarcomas and give specific examples of successful and proposed approaches to targeted therapy for this disease.

Key Words: Sarcoma, Molecular, Targeted, Personalized therapy

1. INTRODUCTION

1.1. Overview of Soft Tissue Sarcomas and Bone Tumors

In the United States there are an estimated 15,000 new cases of tumors arising from connective tissues leading to approximately 5000 deaths per year (1). These tumors are heterogeneous and rare, making this entity a diagnostic challenge for pathologists. For instance, some sarcomas have been misclassified as “benign” despite well recognized risks of local recurrence, invasion, or metastasis. Thus, variations in pathologic definitions have made it difficult to obtain the exact number of patients with sarcomas. Despite the low incidence, sarcomas are within the same order of magnitude as myeloma, cervical carcinomas, gliomas, and carcinomas of the esophagus; and it occurs more frequently than testicular carcinomas.
or Hodgkin’s disease. Most patients with sarcoma are in the younger years of their lives; thus, the disease is a significant public health problem despite its low incidence.

Progress in the treatment of STS and BTs from 1970 to 1990 included improvements in histopathologic classification, staging, use of radiotherapy as an adjunct to other modalities, surgical advances in functional preservation, and identification of doxorubicin and ifosfamide as active systemic therapy. Doxorubicin and ifosfamide are the two most widely used agents for the treatment of advanced STSs, giving an overall response rate of 64% (2) when used in combination at full therapeutic doses. A more recent regimen with activity in STS is the combination of gemcitabine with docetaxel, resulting in an overall response rate of 50% (3). BTs are treated with regimens including doxorubicin, ifosfamide, cisplatin, and methotrexate (4,5). After failure of these agents, the therapeutic options are limited. Although efficacious, some of these therapies are not commonly used by community oncologists and may be best administered at a tertiary referral center.

Given the rarity of STS, most clinical trials have grouped all tumor subtypes together when evaluating both existing and experimental drugs. Yet, progress in translational research over the last two decades has identified a number of cytogenetic and immunohistochemical properties that enables STS to be diagnosed more precisely. Similar to the gradual transition from a morphology-based to a genetic-based system that has occurred for lymphomas, better delineation of STS subtypes has allowed improved understanding of their unique prognosis, response to chemotherapy, and mechanisms of resistance. That information is critically important, as it helps avoid treating certain tumor types—e.g., alveolar soft-parts sarcoma, conventional skeletal chondrosarcoma, gastrointestinal stromal tumor (GIST) and clear cell sarcoma—with standard sarcoma chemotherapy regimens to which they are unlikely to respond and opens the door to future drug development targeted to the unique molecular aberrations responsible for their malignant behavior. Therefore, improved treatment of these chemotherapy-resistant sarcomas will require the novel discovery of drugs that are both more effective and safer to administer.

Research has begun to unravel the molecular etiology of these tumors by identifying specific molecular alterations that are acquired during sarcomagenesis. Several act directly to induce features typical of malignant transformation, including growth factor independence, resistance to apoptosis, angiogenesis, cell cycle dysregulation, loss of genomic integrity, and the ability to invade and metastasize (6). The ability to inhibit these molecular perturbations represents a therapeutic opportunity to counteract the driving factors that promote growth and metastasis of STSs and BTs (Table 1). In this chapter we give an overview of the targeted therapy of sarcoma in the context of tumor cell characteristics as they apply to specific sarcoma histologic subtypes.

1.2. Molecular Alterations in Soft Tissue Sarcomas and Bone Tumors

1.2.1. General Information

As used for other more homogeneous solid tumors, sarcomas have traditionally been staged using AJCC criteria incorporating tumor size, depth, nodal status, grade, and extent of disease. The prognostic and clinical relevance of this ‘one size fits all’ staging approach to STS is less than ideal, however, as it fails to incorporate equally important factors such as STS subtype or location. This process of grouping of STS by name rather than by their diverse tissue of origin, seems to have hampered studies of biology, prognostic markers, and targeted therapy. For example, low response rates to conventional or experimental therapies in studies combining sarcoma histologic subtypes may have obscured higher