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Pazopanib a tyrosine kinase inhibitor with strong anti-angiogenetic activity: A new treatment for metastatic soft tissue sarcoma

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Contents

Abstract

Soft tissue sarcomas (STS) are rare tumors with mesenchymal origin, accounting for 1% of all human cancer. Local control of STS can be obtained through the use of surgery and radiotherapy. In about 40% of these patients, disease will recur at distant sites, and of these more than 90% will die because of this aggressive malignancy. In advanced and/or metastatic STS patients treated with anthracycline-based regimen the median overall survival is about 12 months, and it has remained unchanged during the last 20 years. Clearly, this strongly suggests the need for discover more active compounds in STS, such as imatinib in GIST or dermatofibrosarcoma patients. In this paper we describe the crucial role of angiogenesis mechanisms in sarcomas development and progression. Consequentially, we focus on pazopanib, a novel multitargeted tyrosine kinase inhibitor with anti-angiogenic activity, mainly due to VEGFR2 pathway interference. We also analyze principal completed trials leading pazopanib approval in sarcomas pretreated patients.

Keywords: Pazopanib; Angiogenesis; Soft tissue sarcoma; Vascular endothelial growth factor (VEGF); Targeted therapy; Tyrosine kinase inhibitor (TKI)

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1. Introduction

Sarcomas are a rare and heterogeneous group of tumors with mesenchymal origin. Historically, they were grouped into two main types according to tumor location: soft tissue sarcoma (STS) and primary bone sarcoma (PBS) [1].

An alternative sarcoma genetic-based classification evolved upon the subsequent identification of its molecular and genetic alterations associated with histological subtypes. According to this classification, sarcomas fall into two main categories. The first group is characterized by the presence of tumor-specific translocations, including alveolar rhabdomyosarcoma, myxoid liposarcoma, Ewing's sarcoma and synovial sarcoma. The second group is characterized by complex karyotypes indicative of severe genetic and chromosomal instability, and it is represented by leiomyosarcoma, malignant fibrous histiocytoma and osteosarcoma [2].

STS group comprises more than 50 different tumor entities that exhibit great differences in terms of genetic alterations, pathogenesis, and clinical behavior [3].

It can arise almost anywhere in the body, about 43% occurs in the extremities (e.g., arms, legs); 34% occurs in and around the internal organs (e.g., uterus, heart); 10% occurs in the trunk (e.g., chest, back); and 13% occurs in other locations [4]. In very rare cases, these tumors develop in the gastrointestinal tract, and this group of disease is called gastrointestinal stromal tumors (GISTs).

Local control of STS (accounting for 1% of all human cancers) can be obtained through the use of surgery and radiotherapy. In approximately up to 40% of these patients disease will recur at distant sites, and of these more than 90% ultimately will die because of this aggressive malignancy [5,6]. The probability of the tumor to metastasize is directly correlated with the histological grade, which is the most important predictive factor for distant metastases. In advanced and/or metastatic STS the median overall survival (OS) is about 12 months, and it has remained unchanged during the last 20 years. Clearly, this strongly suggests the need for discover more active compounds in this setting of patients [3,6].

Recent advances have refined systemic treatment strategy for some relatively rare and unusual sarcomas forms (dermatofibrosarcoma or GIST) that are currently best treated with targeted therapies, such as imatinib mesylate [5]. However, in the vast majority of cases, both epirubicin (or doxorubicin) and ifosfamide remain the backbone of chemotherapy in patients with locally advanced or metastatic STS. They are the best single agents with proven activity and possibly dose–response curve [7]. Combination chemotherapy regimens have not demonstrated improved survival compared with single agents [5]. Given that the primary aim is palliation, it is of major importance that drug-related adverse events (ADRs) do not outweigh the potential benefits of chemotherapy. For these reasons, doxorubicin remains the standard of care in this patient population.

Obviously, further more effective agents need to be identified to improve outcome of STS patients [8].

2. Angiogenesis

Angiogenesis is a complex process, mainly mediated by endothelial cells, consisting in the formation of new blood capillaries from existing vessels [9–12]. It is well regulated by the balance between, on the one hand, several angiogenesis stimulators, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiopoietins, platelet derived growth factor (PDGF), angiopoietins, tryptase, and, on the other, some angiogenesis inhibitors, including thrombospondin, angiostatin, and endostatin [13–19].

Angiogenesis in addition to being involved in normal physiological processes, it plays a crucial role in tumor growth, invasion and development of metastasis [20,21].

Unlike what occurs during the normal angiogenesis, in tumor angiogenesis the balance of positive and negative angiogenesis factors towards the positive regulators the newly formed vessels are immature with numerous openings along their walls and highly disorganized due to bizarre form [22].

With special regard to VEGF and PDGF, they bind to the external domain of transmembrane receptors with intracellular tyrosine kinase activity stimulating in turn endothelial cells proliferation, migration, and inhibiting apoptosis [13–19].

The VEGF receptors (VEGFRs) are a family of tyrosine kinase (TK) receptors. Currently, three VEGFR subtypes have been identified: VEGFR-1, also known as Flt-1 (fms-like TK1); VEGFR-2, also known as KDR (kinase insert domain-containing receptor TK); and VEGFR-3, also known as Flt-4 (fms-like TK4). These receptors are present in the tumor microenvironment stromal and endothelial cells [13].

The PDGF receptor (PDGFR) tyrosine kinase family comprises the PDGFR, c-Kit and Flt-3. The PDGFR family exerts its effects through 2 intracellular TK receptors, α and β, after ligand binding at the extracellular domain and receptor dimerization [13,20]. The main pathological effect of PDGFR activation is the cellular proliferation and migration, and it is usually done through the mutational auto-activation of PDGF and PDGFR (i.e. in dermatofibrosarcoma protuberans, GIST and hypereosinophilic syndrome) [20].

Recently, it has been demonstrated that in sarcomas the interaction between VEGF and its receptor (VEGFR2) involved in angiogenesis plays a crucial role in tumor progression [25]. In fact, increased VEGF serum levels are significantly related with worse prognosis and shorter survival especially in leiomyosarcoma patients [22–24,26,27]. Two studies found that high VEGF serum levels correlated strongly with the poorest differentiated STS [28,29]. There are controversial results about VEGF expression role as independent predictor factor of OS or disease-free survival (DFS) [29,30]. Moreover, Shintani et al. demonstrated that