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Current Perspective

Olaratumab in soft tissue sarcoma – Current status and future perspectives

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Abstract Recent randomised phase II trial data have indicated that the addition of olaratumab, a novel monoclonal antibody against platelet-derived growth factor receptor alpha (PDGFRα), to doxorubicin confers an unprecedented improvement in overall survival to patients with anthracycline-naïve advanced soft tissue sarcoma. However, this result was disproportionate with progression-free survival and response rate, and consequently there are unanswered questions regarding the precise mechanism of action of olaratumab. While preclinical data show that olaratumab specifically inhibits PDGFRα-mediated oncogenic signalling with attendant anti-tumour effects, a lack of correlation between pharmacodynamics markers of PDGFRα inhibition and clinical benefit from olaratumab suggest other mechanisms beyond modulation of downstream PDGFRα molecular pathways. Proposed mechanisms of olaratumab activity include engagement of anti-tumour immune responses and alterations of the tumour stroma, but these require further evaluation. Meanwhile, the drug-specific contribution of cytotoxic agents to olaratumab-containing combinations has yet to be characterised. Ongoing and future preclinical and translational studies, coupled with the anticipated results of a phase III trial that has completed enrolment, should provide greater insight into the efficacy and mode of action of olaratumab in soft tissue sarcomas.

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1. Introduction

Soft tissue sarcomas (STS) are a group of rare and heterogeneous malignant tumours of mesenchymal origin that represent around 1% of adult malignancy and encompass a broad range of clinical phenotype and underlying biology. Doxorubicin-based chemotherapy has been the standard for first-line treatment of advanced STS for decades, with associated median overall survival (OS) consistently reported at 12–18 months [1]. Meanwhile, over 20 years of clinical studies in advanced STS have rarely provided definitive evidence of survival benefit for investigative agents [2–5]. However, in July 2016, a major breakthrough was achieved by the results of the JGDG study. In this open label phase Ib and randomised phase II trial, olaratumab, a monoclonal antibody (mAb) directed against platelet-derived growth factor receptor-alpha (PDGFRα), was combined with standard doxorubicin chemotherapy in anthracycline-naïve advanced STS [6]. In the phase II component, a near-doubling of median OS was seen in patients who received combined olaratumab–doxorubicin, leading to the accelerated approval of olaratumab in this setting. However, a discrepancy between a large improvement in OS and only modest improvement in disease control end-points in the JGDG trial has given rise to unanswered questions regarding the activity of olaratumab. In this perspective article, we outline the therapeutic rationale and clinical data for olaratumab in advanced STS, before exploring potential explanations for the unresolved enigma of an agent that appears to confer a highly significant survival benefit without a corresponding improvement in disease control.

2. Olaratumab: a novel PDGFRα-targeting antibody

PDGFRα is a receptor tyrosine kinase (RTK) that engages downstream pathways that play important roles in mesenchymal stem cell differentiation and vascular endothelial growth factor–mediated angiogenesis [7]. Overexpression and activating mutations of *PDGFRA* in cancer have been shown to contribute to tumour development, proliferation, metastasis and establishment of a tumour-supporting microenvironment [8–10]. In STS, increased tumour expression of PDGFRα corresponds with higher histological grades and poor prognosis [11]. A range of tyrosine kinase inhibitors with activity against PDGFRα have been evaluated in advanced STS, whereas pazopanib attained approval in the post-1st line setting based on phase III trial evidence of progression-free survival (PFS); but not OS benefit over placebo, a number of other related agents have demonstrated generally disappointing efficacy [12,13].

Olaratumab is a human immunoglobulin G subclass 1 mAb with selective, high affinity binding to the extracellular domain of PDGFRα, disrupting receptor-ligand interactions with resulting downregulation of downstream signal transduction [6,7,14]. Olaratumab has *in vitro* and *in vivo* activity in reducing proliferation and progression of numerous cancer cell lines including sarcomas [14,15]. In addition, combination of olaratumab with doxorubicin resulted in greater inhibition of tumour growth compared with doxorubicin alone in xenograft models of human osteosarcoma [16].

Two open-label dose-escalation Phase I studies evaluated olaratumab as a single agent in patients with advanced solid tumours (Table 1). In both the earlier U.S. and later Japanese studies, the drug was well tolerated and without dose-limiting toxicities [17,18] (Tables 1 and 2). No objective radiological responses were observed in either study—a best response of stable disease was seen in 12 (63%) patients in the US phase I, and in 7 (44%) patients in the Japanese trial.

Based on preclinical evidence of potential synergy with doxorubicin, the combination of olaratumab with chemotherapy was investigated in advanced STS in the JGDG study. Fifteen patients were enrolled in the phase Ib component, and all were treated with olaratumab (15 mg/kg on D1+D8 q3w) and doxorubicin (75 mg/m^2 on D1 q3w) for up to eight cycles, with the addition of dexrazoxane during cycles 5–8, at the discretion of the treating investigator. Patients then continued with olaratumab monotherapy until disease progression. Having satisfactorily met the primary safety end-points of the initial phase 1 b stage, the study rolled out to an open-label phase II stage, with patients randomised 1:1 to receive doxorubicin alone or in combination with olaratumab as per phase Ib schedule. The phase II study was designed to detect a 50% improvement in median PFS (hazard ratio [HR] 0.67) with 80% power and two-sided significance level of 0.20.

In the intention-to-treat (ITT) analysis of 133 randomised patients, a significant improvement in the primary end-point of investigator-assessed PFS was seen in the olaratumab–doxorubicin arm, albeit at the prestated significance level (HR 0.672, 95% confidence interval [CI] 0.442–1.021, p = 0.0615), while there was a non-significant increase in objective response rate from 11.9% to 18.2% between control and investigational arms respectively (p = 0.34). However, the 2-month improvement in median PFS (4.1 months in the control arm vs. 6.6 months in olaratumab arm) was dwarfed by a 12-month improvement in median OS (14.7 vs 26.5 months; OS HR 0.46; 95% CI 0.30–0.71; p = 0.0003). OS benefit from olaratumab-containing therapy was seen across all analysed pre-planned and post-hoc subgroups, including prospectively stratified leiomyosarcoma vs. other histological subtype subgroups. Prospective IHC assessment of tumour PDGFRα expression was performed using an assay later recognised as being insufficiently specific. A post-hoc repeat analysis of tumour PDGFRα using a more specific IHC assay found that most enrolled patients' tumours (67%) were PDGFRα negative, whereas PDGFRα expression was not found to be associated with OS or PFS.