SARCOMA

Olaratumab — really a breakthrough for soft-tissue sarcomas?

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In a recent study, the addition of olaratumab to doxorubicin chemotherapy for patients with soft-tissue sarcoma resulted in prolongation of progression-free survival by only 2.5 months, but an overall survival benefit of 11.8 months; the large disparity between these outcomes raises important questions. We discuss these results in relation to those of other trials, and the implications for sarcoma therapy.

Refers to Tap, W. D. *et al*. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet* http://dx.doi.org./10.1016/S0140-6736(16)30587-6 (2016).

In the past 20 years, important breakthroughs have been made in the treatment of soft-tissue sarcoma (STS), and none more clinically significant than the introduction of effective tyrosine kinase inhibitors for patients with gastrointestinal stromal tumours with activating mutations in *KIT* or *PDGFRA*[1]. Such advances have, however, proved to be the exception rather than the rule: subsequently, few clinical studies have demonstrated a survival benefit with experimental therapies. Nevertheless, a report published in June 2016 by Tap *et al*.[2] seems to herald a major therapeutic breakthrough. In this open-label phase Ib and randomized phase II trial involving adults with advanced-stage STS, combination therapy comprising doxorubicin and olaratumab, a monoclonal antibody that inhibits PDGFRα, was compared with doxorubicin monotherapy — the current standard of care; in the phase II part of the study, 133 patients were randomized in a 1:1 ratio[2]. Patients in the combination arm had a median overall survival of 26.5 months, compared with 14.7 months for those treated with doxorubicin monotherapy (hazard ratio (HR) 0.46; $P = 0.0003$)[2]. By contrast, PFS was extended by only 2.5 months in the olaratumab arm (6.6 months versus 4.1 months)[2]. Thus, the primary end point of the study, a 50% increase in PFS, was met, but this improvement was not conventionally significant by investigator assessment (HR 0.67; $P = 0.0615$), or independent radiological review (HR 0.67; $P = 0.1208$)[2].

Interestingly, just 2 months earlier, in April 2016, results of phase III trial of eribulin versus dacarbazine in patients with leiomyosarcoma or liposarcoma demonstrated a 2-month median overall survival benefit for the eribulin cohort (13.5 months versus 11.5 months; HR 0.77; $P = 0.0169$), with no difference in the median PFS (2.6 months in both groups; HR 0.88; $P = 0.23$)[3]. Eribulin treatment mainly benefitted the patients with liposarcoma (HR 0.51), with limited or no benefit in patients with leiomyosarcoma (HR 0.93). As a result, eribulin has been approved by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) for the treatment of liposarcoma. Nevertheless, without a prolongation of PFS, no clear explanation is available for the overall survival benefit associated with eribulin. Conversely, many studies in patients with STS have demonstrated PFS

improvements, but no increase in overall survival[4,5]. Similarly, large phase III trials have failed to confirm therapeutic benefits seen in randomized phase II studies, including unpublished studies of palifosfamide and evofosfamide[6,7]. Various explanations for the lack of an overall survival benefit have been proposed, not least the effects of post-protocol treatment.

Why are trial results so inconsistent in STS? In particular, what factors underlie the considerable disparities between the observed PFS and overall survival benefits? An answer might lie in the sheer diversity of STS diagnoses: this disease can be classified into 70 different histological subtypes[8], and this huge heterogeneity creates major problems when designing and interpreting clinical trials. In a small trial (*n* = <200), imbalances in disease biology between treatment groups can have major effects on the findings, potentially resulting in an apparently major benefit that will not subsequently be confirmed in a larger, well-balanced phase III trial. Could this phenomenon have occurred in the olaratumab study? Some imbalances did exist: for example, the proportion of patients with undifferentiated pleomorphic sarcoma, an aggressive STS subtype, was 15% in the combination arm, but 21% in the monotherapy arm[2]. Moreover, more women were included in the combination arm (61% versus 51%)[2], perhaps indicating an excess of patients with uterine leiomyosarcoma. Leiomyosarcoma is itself a heterogeneous group of diseases, within which uterine leiomyosarcoma has a relatively good prognosis[9]. A marked imbalance also occurred in the 'other' disease category, which included 17 patients (26%) in the combination arm, but only six patients (9%) in the monotherapy arm[2]. Importantly, a number of 'other' disease subtypes associated with indolent behaviour and prolonged survival were represented in the combination arm, but not the monotherapy arm, including alveolar soft part sarcoma, endometrial stromal sarcoma, extraskeletal myxoid chondrosarcoma, fibrosarcomatous change in dermatofibrosarcoma protuberans, solitary fibrous tumour, and myxoid chondrosarcoma. These imbalances might have had a substantial effect on overall survival.

Can explanations be drawn from the study design? Tap *et al*.[2] randomly assigned patients to receive eight 21-day cycles of doxorubicin given at 75 mg/m^2 on day 1, with or without olaratumab at 15 mg/kg on days 1 and 15. In the combination arm, patients with stable disease response or a better could continue on olaratumab after stopping doxorubicin, whereas patients initially assigned doxorubicin monotherapy could only receive olaratumab after disease progression. A potential bias in favour of continuing treatment with the novel combination was also evident: 21 patients discontinued treatment for radiological disease progression in the combination arm, but only 12 other patients stopped treatment early[2]; by contrast, although 27 patients in the monotherapy arm discontinued treatment for radiological progression and six for symptomatic progression, remarkably, 27 patients stopped treatment early for a variety of other reasons[2]. Indeed, only 7% of patients discontinued combination therapy compared with 13% who discontinued monotherapy. This difference in

frequency of termination of study treatment for reasons other than disease progression occurred in spite of the combination regimen being more toxic, with a higher incidence of grade ≥3 adverse effects (80% versus 69%), including bone marrow toxicity, nausea, cardiac dysfunction, and decreased appetite[2]. A potential explanation is that patients in the combination treatment arm knew they were receiving a potentially effective experimental agent and were reluctant to stop treatment. In addition, olaratumab therapy upon disease progression after doxorubicin monotherapy was considerably shorter in duration than maintenance treatment after combination therapy (median of four versus nine cycles)[2]. Of note, crossover to olaratumab monotherapy after disease progression was reported under the category of 'other' post-treatment therapy, despite being permitted in the protocol and, more importantly, despite the experimental nature of this treatment[2]. Following protocol therapy, patients in the combination arm were almost twice as likely to receive gemcitabine plus docetaxel than those in the monotherapy arm, and were more likely to receive pazopanib and trabectedin[2] — all of which are known to be active second-line treatments. As mentioned previously, effective post-trial therapy can negate an overall survival advantage; however, post-protocol therapy can also lead to an imbalance in favour of the experimental treatment if a systematic bias results in crossover of patients in the control arm to an experimental treatment that is less effective as monotherapy than subsequent chemotherapy. Thus, the differences in post-protocol therapy are potentially important, considering that many patients in the doxorubicin arm initially received second-line olaratumab monotherapy, which only modestly improves PFS even when combined with doxorubicin in the first-line setting[2], and were less likely to receive second-line treatments with proven effectiveness than those in the combination arm. Finally, no statement is made by Tap *et al*.[2] about post-protocol local treatments, such as surgery and radiotherapy, that are relatively commonly applied in patients with STS, and might have influenced the results.

Another imbalance, which almost certainly occurred by chance, was the number of deaths that were recorded as neither drug-related nor categorically related to disease progression: six in the doxorubicin arm, but none in the combination arm.

The precise mechanism of action of olaratumab remains unknown. Interestingly, Tap *et al*.[2] found no correlation between tumour PDGFRα positivity and outcome (HR 0.64 95% CI 0.31–1.33), and, indeed, reported that negative expression was favourable (HR 0.40 95% CI 0.21–0.73)[2], which does not support PDGFR inhibition in the tumour as the prime mechanism of action. As they discussed, however, the immunohistochemistry assay used to assess PDGFRα expression was, in hindsight, not very specific and needs improvement. The authors hypothesized that the disparity between the PFS and overall survival benefit indicates that the drug could induce a persisting alteration in tumour–stromal interactions, but that is currently sheer speculation. This result is, nevertheless, reminiscent of findings with immunomodulatory therapy: a similar discrepancy between PFS and overall survival has been reported with use of the immune- checkpoint inhibitor ipilumumab in

patients with melanoma[10]. In that study, prolonged survival was seen in a substantial proportion of patients in spite of early radiological disease progression[10]. Does olaratumab possibly exert an immunological effect? Translational studies to explore such mechanisms of action, and others, would be useful.

In conclusion, the findings of this relatively small trial of olaratumab, although promising, raise a number of questions, especially regarding the large discrepancy between PFS and overall survival. Differences in treatment duration for reasons other than radiological progression, imbalances both in histological subtypes and post-protocol therapy, and deaths due to unrelated adverse events could all have contributed to the result. Eli Lilly have been granted 'Priority Review' status for olaratumab by the FDA and the agent is currently being reviewed by the EMA under an accelerated assessment schedule. What that actually means in terms of access of patients with sarcoma to the drug is currently unclear, but provisional approval could be granted. What is undoubtedly the case is that the real value of olaratumab in the treatment of STS will only be known once the results of the phase III trial of this agent, which is currently close to completion (NCT02451943), are published in a few years' time.

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Competing interests statement

I.J. has received an honorarium from Eli Lilly for attendance at an advisory board meeting; however, the views expressed in this article are his own. I.J. has also received honoraria from Ariad, Amgen, Bayer, GSK, PharmaMar, Clinigen, and Nektar. W.T.v.d.G. has received a speakers' fee from Eli Lilly for an educational presentation on sarcoma, and has received research grants from GSK and Novartis.

Author biography

Ian Judson graduated in with a BA in Natural Sciences from Cambridge University, UK, in 1972, studied medicine at the King's College Hospital Medical School and medical oncology at the Royal Marsden Hospital in London, UK. He was awarded an MD from Cambridge University in 1988 for work on cancer pharmacology, was appointed Senior Lecturer at The Institute of Cancer Research, Sutton, Surrey, in 1989, and became Professor of Cancer Pharmacology in 2001. He has published more than 250 peer-reviewed papers plus numerous reviews and editorials, focused on new anticancer drug development and soft-tissue sarcomas. He has conducted clinical trials in sarcoma, including the initial studies of imatinib in the treatment of gastrointestinal stromal tumour. He has held the positions of President of the Connective Tissue Oncology Society, President of the British Sarcoma Group, Chairman of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG), of which he is currently Treasurer, and was until recently Head of the Sarcoma Unit at the Royal Marsden.

Winette T. van der Graaf obtained her PhD on multidrug resistance in cancer in 1993, and then trained and worked as medical oncologist at the University Medical Centre of Groningen in the Netherlands. In 2007 she was appointed as Professor of Medical Oncology at Radboud University Medical Centre (Radboudumc) in Nijmegen, Netherlands. From 2010–2015, she was Chair of the Department of Medical Oncology at Radboudumc, and was theme lead for Rare Cancer until she moved to the Institute of Cancer Research in London, where she was appointed as Professor of Personalised Oncology and team leader of clinical and translational sarcoma research. At the same time she joined the Sarcoma Team of the Royal Marsden Hospital. She has co-authored more than 350 publications. She initiated the Dutch AYA programme for young patients with cancer and has been Chair of the EORTC STBSG between 2011 and 2014. Currently she is a board member of the EORTC.