that selumetinib shows great activity in both NF1-related paediatric low-grade glioma and paediatric low-grade glioma associated with *BRAF* alterations. However, and particularly in the latter group, most patients experience progression during treatment or after discontinuation, suggesting that either the duration of treatment is not long enough or that single-agent selumetinib is not sufficient to prevent further tumour progression. Since event-free survival with selumetinib seems to be comparable with that observed with chemotherapy,[2,5] an important question is whether combination of selumetinib with chemotherapy or other agents such as mTOR inhibitors should be considered as the experimental arm in future trials.

Finally, what accrual rate do we expect in these trials, considering the many advantages of selumetinib or other MEK inhibitors over chemotherapy, such as promising activity, oral administration, limited number of clinic visits, no risk of immunosuppression, no hair loss, and potential visual benefit? How many families will try to get the medication through their insurance (eg, in the USA) after the publication of this phase 2 trial?

We should also keep in mind that 80% of children with NF1 and 40% of children without NF1 with paediatric low-grade glioma treated with one line of chemotherapy are doing well and do not require any further treatment.[2] Considering the major financial implications of a complete shift in the treatment of paediatric low-grade gliomas, one might wonder whether the forthcoming COG trials are really asking the right question.

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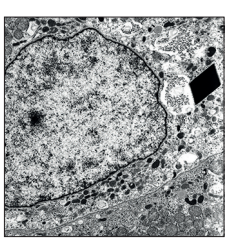
Cediranib for alveolar soft part sarcoma: a randomised study in relation to clinical practice

In *The Lancet Oncology*, Ian Judson and colleagues, investigators of the Cediranib for Alveolar Soft Part Sarcoma (CASPS) trial, report on a randomised, placebo-controlled, phase 2 trial testing the tyrosine-kinase inhibitor cediranib in metastatic alveolar soft part sarcoma (ASPS).[1] The study was formally positive, although the clinical benefit of cediranib was small.

ASPS is a rare subtype of sarcoma that mostly affects young adults, with a high frequency of distant metastasis leading to poor long-term survival despite a typically indolent disease course. Activity of cediranib in metastatic ASPS has previously been shown in a phase 2 study in gastrointestinal stromal tumours and sarcomas, including six patients with ASPS, four of whom had a durable partial response and one had prolonged stable disease.[2] Additionally, in a National Cancer Institute study[3] of 46 patients (43 evaluable) with ASPS, 15 (35%) achieved a Response Evaluation Criteria in Solid Tumour (RECIST)-defined overall response, 26 (60%) stable disease, and 36 (84%) controlled disease (ie, stable disease and partial responses) at 24 weeks. In the CASPS trial, 32 patients with ASPS were treated with cediranib and 16 were given placebo, and after 24 weeks (or sooner if disease progression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occurred) all patients on placebo were crossed over to cediranib. With a median follow-up of 34·3 months (IQR 23·7–55·6) at the time of data cutoff for these analyses (April 11, 2018), this study met its primary endpoint, which was based on tumour response, defined as percentage change in the median sum of the longest diameters of target marker lesions at 24 weeks. Judson and colleagues aimed to detect a 20% difference in favour of cediranib, and found a significant difference in the median sum of the diameters of target marker lesions of 22% at 24 weeks (–8·3% [IQR –26·5 to 5·9] in the cediranib group *vs* 13·4% [1·1 to 21·3] in the placebo group; one-sided p=0·0010), even though the number of patients enrolled was relatively low (overall n=48, evaluable population n=44). Unexpectedly, of the evaluable participants at week 24 (n=28), 11% (n=3) achieved a RECIST defined partial response and 50% (n=14) had stable disease, results that are inferior to previous phase 2 studies of cediranib.[2,3]

This randomised study treated fewer patients with ASPS with cediranib than the NCI phase 2 study.[3] Our question is to what extent the randomised study design, which selected response as the primary endpoint in this specific population and tested this class of drugs, increased the reliability of the CASPS trial results compared with other uncontrolled, phase 2 studies. Concerns about spontaneous disease stabilisation and slow progression of metastatic ASPS were the basis for conceiving the placebo-controlled design and for requiring evidence of progression in the previous 6 months among the entry criteria. This design required a longer study duration than other uncontrolled, phase 2 studies and made cediranib available to fewer patients, although admittedly after 24 weeks the patients in the placebo group were switched to cediranib. However, 44% (n=7) of patients in the placebo group had stable disease at 24 weeks, suggesting that the requirement of disease progression in the previous 6 months did not add substantially to the study design. Patients in the placebo group did not show spontaneous regression, by contrast with the placebo group in a randomised trial[4] testing sorafenib in treatment-refractory and advanced desmoid tumours, a mesenchymal neoplasm notable for its different natural history.

Although, in our opinion, progression-free survival would have been a more appropriate primary endpoint than response for this study, more patients would have been needed to detect a longer progression-free survival in the cediranib group, challenging the completion of the trial in such a rare disease. In this study, cediranib did not significantly improve progression-free survival compared with placebo, but the study was not powered to test this difference and therefore cannot conclude on this endpoint. However, RECIST responders had a valuable median duration of response of 16·0 months (IQR 15·7–26·0). In other words, from the clinical point of view, few patients had relatively long-lasting responses.

The CASPS trial provides evidence that anti-angiogenics are active in ASPS, although they might not have been created equally, and cross-resistance between them might be restricted. So far, the only antiangiogenic approved in sarcomas is pazopanib,[5,6] as second-line therapy, leaving doxorubicin as the standard first-line therapy, although ASPS is refractory to anthracyclines. Ongoing studies are testing new antiangiogenics (eg, anlotinib [NCT03016819])[7] and immunotherapy[8,9] alone or in combination for metastatic ASPS, fostering new hopes in this patient population. We do not believe that future trials in such a rare tumour would need a placebo-controlled group like in the CASPS trial, for all the limitations mentioned here, and because antitumor activity can be studied in uncontrolled, phase 2 trials. Although the development of innovative response criteria is a good idea in theory, response duration and progression-free survival are the most clinically meaningful endpoints to assess the effect of new therapies.

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