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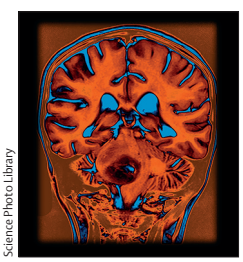
Selumetinib in paediatric low-grade glioma: a new era?



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Since the first publication on the activity of the carboplatin–vincristine combination in paediatric low-grade glioma in 1993,[1] chemotherapy has become the mainstay of treatment for this condition, particularly in young children (aged 0–10 years). However, 5-year event-free survival in the non-neurofibromatosis type 1 (NF1) population is in the range of 40% and most patients require several lines of treatment.[2] Patients with NF1 have a longer event-free survival than those without NF1, ranging between 65% and 85%.[2] No chemotherapy protocol has shown superior activity, and although the chemotherapeutic management of paediatric low-grade glioma varies between cooperative groups, countries, and institutions, overall, it follows the same principles.[3]

Over the past 15 years, research has shown that nearly all paediatric low-grade gliomas have alterations that activate the RAS-MAP kinase pathway.[2] The most common alterations are loss of neurofibromin in the context of NF1, and in non-NF1-related paediatric low-grade glioma the fusion and tandem duplication of *BRAF* with *KIAA1549* and the *BRAF*^{V600E} mutation.[4] These discoveries have provided the possibility to target the RAS-MAP kinase pathway, in particular with MEK inhibitors, which function downstream of RAF and should be effective in NF1-related paediatric low-grade gliomas and paediatric low-grade glioma harbouring either *BRAF* alteration.[4]

In *The Lancet Oncology*, Jason Fangusaro and colleagues[5] report the results of two of six strata of patients (aged 3–21 years) with recurrent, refractory, or progressive paediatric low-grade glioma from a phase 2 trial of selumetinib, a selective inhibitor of MEK1/2, which had shown promising activity in a phase 1 study.[6] Stratum 1 comprised 25 patients harbouring *BRAF* alterations: nine achieved a partial response, nine had stable disease, and seven had progressive disease. The NF1 stratum (stratum 3) comprised 25 patients, all of whom had some evidence of tumour shrinkage, including ten partial responses. In stratum 1, 14 (56%) of 25 patients had progression (nine during treatment and five after completion), whereas in stratum 3 only one patient progressed while on therapy and seven after completion of therapy. Most toxic effects were moderate, although 18 (36%) of patients (ten in stratum 1 and eight in stratum 3) required a dose reduction of selumetinib. These results confirm the promising activity of selumetinib in paediatric low-grade glioma.

Visual outcome data were also encouraging: among ten patients tested, all from stratum 3 (NF1), two experienced improvements in visual acuity and eight stable vision. Although these results seem to compare favourably with those from a previous study of conventional chemotherapy,[7] the major differences between the studies in terms of sample size, design, line of treatment, and age preclude any definitive conclusions. Additionally, no visual outcome data were provided on the ten patients with hypothalamic or optic pathway tumours treated in stratum 1. Future trials must mandate more functional outcome data on all patients to better investigate the potential advantage of selumetinib over chemotherapy.

Despite these encouraging results, some questions remain. 9 years have passed since the initiation of the phase 1 trial. Why did it take so long to complete these two trials? Was this due to a design issue, slow accrual, or competing trials? Why does it take so long to have such an effective drug approved when it took less than 5 years for everolimus or larotrectinib?[8,9]

Also, why is the next step the development of two randomised phase 3 Children's Oncology Group trials comparing selumetinib with standard chemotherapy in patients with both NF1-associated and sporadic paediatric low-grade gliomas? The design of these trials seems outdated already. We know already

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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I declare no competing interests.

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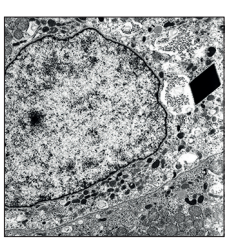
Cediranib for alveolar soft part sarcoma: a randomised study in relation to clinical practice

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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