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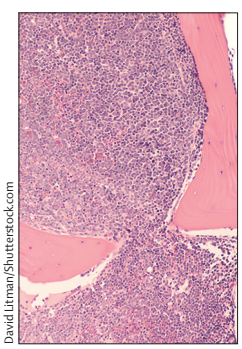
Targeted therapies make room, anti-CD79b agents are coming



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Several molecules are being investigated as targets of new anti-lymphoma therapies, such as bispecific antibodies, antibody–drug conjugates (ADC), and chimeric antigen–receptor T cells. B-cell receptor components represent important targets, and some anti-B-cell receptor agents have been established as standards of care in selected lymphomas. However, B-cell receptor molecules are unsuitable targets for antibody-based therapies because they are located inside cells; CD79 is an exception. CD79 (composed of subunits CD79a and CD79b) is a heterodimeric signal-transduction component of the B-cell receptor, ubiquitously expressed in mature B-cell lymphomas and placed on the cell surface by the earliest committed B-cell progenitors before expression of immunoglobulin μ. Antibodies to CD79b induce negative cell signals and suppress response to T-cell-dependent antigens.[1] However, unconjugated anti-CD79b antibodies induce modest B-cell depletion and show moderate antibody-dependent and complement-dependent cellular cytotoxicity, if any.[2] Conversely, anti-CD79b antibodies might be suitable candidates for ADCs, which are tripartite molecules consisting of a cytotoxic agent conjugated to an anti-tumour antibody by a cleavable linker. Anti-CD79b ADCs are trafficked to a lysosomal-like compartment of B cells as part of antigen presentation,[3] and induce a prolonged and sustained depletion of proliferating B cells.[2] Early clinical studies support these encouraging in-vitro observations, suggesting that anti-CD79b ADCs might be effective therapies against B-cell lymphomas.

In *The Lancet Oncology*, Hervé Tilly and colleagues[4] report a company-sponsored phase 1b–2 trial assessing the safety and activity of an ADC called polatuzumab vedotin—which targets CD79b to deliver monomethyl auristatin E, a small anti-tubulin agent—in combination with cyclophosphamide, doxorubicin, prednisone (CHP), and an anti-CD20 antibody (either rituximab or obinutuzumab) in 82 patients with different B-cell lymphomas. As main contributions, this study showed that the addition of polatuzumab vedotin did not result in higher toxicity than treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab, established the recommended phase 2 dose for polatuzumab vedotin (1·8 mg/kg), and suggested this combination might have activity in lymphomas. Neutropenia and febrile neutropenia were the most common adverse events of grade 3 or worse, and the events of peripheral neuropathy[4]—the main obstacle to the use of polatuzumab vedotin in combination with vincristine—did not seem to be more severe than those reported during administration of CHOP plus rituximab or obinutuzumab.[5] Importantly, 51 (77%) of 66 patients with diffuse large B-cell lymphoma treated with the recommended phase 2 dose achieved a complete response, with similar proportions in patients with germinal-centre and activated subtypes of diffuse large B-cell lymphoma. In line with in-vitro studies,[6] the authors reported no association between tumour response and CD79b expression level, suggesting that target expression is not an informative selection criterion in trials of polatuzumab vedotin.[4] These results suggest that polatuzumab vedotin could play a relevant role in the treatment of diffuse large B-cell lymphoma and provide interesting insights into the development of this promising drug.

Polatuzumab vedotin meets most of the ADC efficacy criteria: it is a high-affinity, humanised antibody with a linker that is stable to hydrolysis and glutathione deconjugation, which prevents the systemic release of monomethyl auristatin E; it has high internalisation capability; and it delivers a payload that is cytotoxic at subnanomolar concentrations. Early

trials (NCT01290549 and NCT01691898) suggest that single-drug polatuzumab vedotin is active, with a response in about 55% of patients with both indolent and aggressive lymphomas. By contrast, no responses were seen in patients with chronic lymphocytic leukaemia, an observation which has been attributed to a lower exposure and faster target clearance than in other indolent and aggressive lymphomas.[7] Synergistic effects with anti-CD20 antibodies associated or not with bendamustine in diffuse large B-cell lymphoma and follicular lymphoma have been reported.[7–9] On these bases, polatuzumab vedotin was granted the breakthrough therapy designation by the US Food and Drug Administration and PRIME designation by the European Medicines Agency for the treatment of relapsed or refractory diffuse large B-cell lymphoma. Nevertheless, the benefit suggested by Tilly and colleagues[4] of the addition of polatuzumab vedotin to immunochemotherapy in patients with diffuse large B-cell lymphoma remains to be confirmed in a large randomised trial. This is the main goal of the POLARIX trial (NCT03274492), which is randomly assigning patients with diffuse large B-cell lymphoma to rituximab–CHP plus polatuzumab vedotin (with placebo vincristine) versus rituximab–CHOP (with placebo polatuzumab vedotin). This is an ambitious objective in view of the fact that none of the recent randomised trials of diffuse large B-cell lymphoma (ie, PYRAMID [NCT00931918], REMARC [NCT01122472], PILLAR-2 [NCT00790036], GOYA [NCT01287741], PHOENIX [NCT01855750], and PRELUDE [NCT00332202]) showed a survival benefit with the addition of a concomitant or adjuvant target drug to rituximab–CHOP. These unsuccessful results might have partly been caused by the difficulties of recruiting some patients with highly-aggressive, fast-growing diffuse large B-cell lymphoma in these trials because of the long screening periods (ie, centralised pathology and molecular investigations) before enrolment, with a consequent smaller proportion of high-risk patients, who are expected to benefit the most from the addition of targeted drugs.

The next steps in the development of polatuzumab vedotin should entail the investigation of the synergistic effects of its combination with other target drugs and the mechanisms of resistance. For example, the expression level of BCL-XL was found to correlate with sensitivity to an anti-CD79b ADC, with the use of Bcl-2 inhibitors strikingly enhancing the in-vivo activity of the anti-CD79b conjugated to monomethyl auristatin E by valine-citrulline.[6] Hence, the combination of polatuzumab vedotin with the Bcl-2 inhibitor venetoclax is being investigated (NCT02611323). Other combinations with lenalidomide (NCT02600897) or atezolizumab (NCT02729896) are also being studied. Potential mechanisms of resistance such as target downregulation, drug transporter expression, trafficking alterations, and abnormalities in signalling pathways should also be investigated in these studies.

In the field of onco-hematology, next-generation drugs have the same mechanism of action but are often more effective and less toxic than first-in-class drugs, by virtue of some chemical changes introduced to improve the therapeutic index. In this setting, iladatuzumab vedotin, another humanised anti-CD79b antibody conjugated to monomethyl auristatin E, has entered the clinic. In a first-in-human study,[10] iladatuzumab vedotin was shown to be safe and associated with a response in 60% of patients with diffuse large B-cell lymphoma. Therefore, it can be anticipated that the role of ADCs targeted to CD79b or other molecules will grow rapidly in lymphoma therapy.

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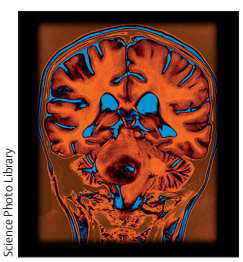
Selumetinib in paediatric low-grade glioma: a new era?



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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