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I declare no competing interests.

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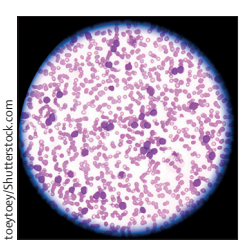
Oral targeted agent versus chemotherapy in acute myeloid leukaemia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In *The Lancet Oncology*, Jorge E Cortes and colleagues[1] present the results of the QuANTUM-R trial, a randomised comparison between the second-generation tyrosine kinase inhibitor quizartinib and standard of care chemotherapy in patients with relapsed or refractory acute myeloid leukaemia carrying an *FLT3* internal tandem duplication (*FLT3*-ITD) mutation. In this difficult clinical situation, patients treated with quizartinib survived for longer than those who received standard chemotherapy. Although the improvement in median survival across all enrolled patients was moderate (6·2 months for quizartinib *vs* 4·7 months for chemotherapy), the results are a substantial step forward in the treatment of acute myeloid leukaemia, since they represent the first published (with the exception of meeting abstracts) randomised evidence that tyrosine kinase inhibition by a single agent can be more efficacious than standard chemotherapy.

Although potentially curable, less than a third of patients with newly diagnosed acute myeloid leukaemia survive the disease. Although a morphological first remission can be achieved in most patients who are treated intensively, the high proportion of patients who relapse is a clinical challenge and the greatest obstacle to a cure.[2] The presence of an ITD mutation in the gene coding region for *FLT3* tyrosine kinase can drive haemopoietic cells towards leukaemia and lead to increased proliferation and resistance to apoptosis in myeloid blasts, corresponding to a high incidence of relapse and poor long-term survival.[3,4] It was hypothesised that small molecules inhibiting *FLT3* signalling could improve the course of disease.[5] First-generation tyrosine kinase inhibitors target several cellular kinases and have restricted single-agent activity. In combination with intensive chemotherapy, sorafenib and midostaurin have shown clinical activity in randomised placebo-controlled trials.[6,7] A significant overall survival benefit in the RATIFY trial[7] led to the approval of midostaurin for first-line treatment of *FLT3*-mutated acute myeloid leukaemia. Quizartinib belongs to a second generation of tyrosine kinase inhibitors that are more specific for *FLT3* and inhibit fewer additional kinases.[5] In early clinical trials enrolling patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia, quizartinib has shown significant single-agent activity, with 24–47% of patients achieving remission.[8] QuANTUM-R shows that this single-agent activity is more efficacious than a standard chemotherapy-based approach in patients with primary refractory disease or early relapse. Indicated by a median survival of 4·7–6·2 months, the medical need in this subgroup of acute myeloid leukaemia is particularly high and the prognosis is unsatisfying even when quizartinib is used. However, it is remarkable

that a single agent that mainly targets the tyrosine kinases *FLT3* and KIT, is orally available, and causes fewer side-effects than standard cytostatic therapy is able to induce a higher proportion of patients achieving remission, to increase the likelihood of allogeneic stem-cell transplantation, and to significantly improve overall survival.

Notably, most remissions achieved in the trial were not accompanied by full haematopoietic recovery, and the beneficial effect of quizartinib on overall survival diminished when patients were censored for allogeneic stem-cell transplantation. Given that similar proportions of transplanted patients were in remission at the time of transplantation, the results show that the significant survival benefit in patients treated with quizartinib was, in part, due to a higher proportion of patients achieving a response than in the chemotherapy group, allowing more patients to proceed to allogeneic transplantation in remission. This finding also shows that single-agent treatment, even with a potent drug such as quizartinib, was not associated with long-term cure for most patients and that less than half of treated patients achieved a remission as a prerequisite for favourable transplantation results.

Will these issues also apply for other second-generation tyrosine kinase inhibitors currently in clinical development, most prominently gilteritinib and crenolanib? Both agents are type I tyrosine kinase inhibitors, which inhibit FLT3 in its active conformation and consequently cause FLT3 inhibition both in *FLT3*-ITD and *FLT3*-TKD mutated disease. As a type II inhibitor, quizartinib only inhibits *FLT3*-ITD. Although *FLT3*-TKD mutations occur in 5% of newly diagnosed acute myeloid leukaemia, these mutations are a common mechanism of resistance acquisition under tyrosine kinase inhibitor treatment of *FLT3*-ITD-mutated acute myeloid leukaemia.[9] Preliminary results[10] of gilteritinib show a similar trend for higher proportions of patients achieving a response and improved overall survival in a clinical trial that is similar in design to the QuANTUM-R study. Owing to favourable proportions of patients achieving remission and time to best response, the US Food and Drug Administration approved gilteritinib therapy for relapsed or refractory *FLT3*-mutated acute myeloid leukaemia in November, 2018, whereas the decision process is ongoing for quizartinib, with a recent majority recommendation by the US Oncologic Drugs Advisory Committee against approval.

The role of tyrosine kinase inhibitors in future treatment algorithms will be determined by published clinical data from the respective clinical trials involving other second-generation tyrosine kinase inhibitors, by the inhibition profile regarding the ITD and TKD, but also by issues of tolerability, dosing and CYP3A inhibition. Single agent treatment might be an option for bridging patients to transplantation with higher chances of success and less toxicity, but single-agent use of second-generation tyrosine kinase inhibitors, such as quizartinib, is, hopefully, only the beginning of a treatment evolution in *FLT3*-mutated acute myeloid leukaemia. The combination with standard chemotherapy in newly diagnosed and relapsed disease, maintenance approaches, and minimal residual disease-guided therapy modification are the most interesting scenarios for future use, which might ultimately lead to long-term remission and cure in most patients.

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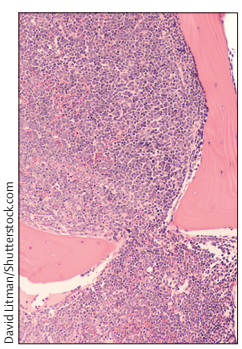
Targeted therapies make room, anti-CD79b agents are coming



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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