How do mTOR inhibitors fit in the landscape of treatment for relapsed acute lymphoblastic leukemia?

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In this issue of *Haematologica*, Tasian *et al.*[1] report the outcomes of a phase I trial of temsirolimus in relapsed/refractory pediatric acute lymphoblastic leukemia (ALL). While the survival rates for children with ALL have improved significantly over time, approximately 20% will relapse and this remains a significant challenge with survival rates <50% following initial relapses and far inferior outcomes for multiply relapsed disease.[2] Historical remission rates after second and third bone marrow relapse are only 44% and 27%, respectively, with a 5-year disease-free survival in second and third remission of 27% and 15%, respectively.[3] Similar response rates and outcomes were reported by Sun *et al.*[4] in a retrospective analysis of over 500 relapsed/refractory ALL salvage treatment attempts at Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) institutions, setting the benchmark for remission rates of approximately 40% after second or subsequent relapse. To address the challenges of relapse and inferior outcomes with intensive cytotoxic chemotherapy alone, molecularly targeted agents with compelling preclinical rationale have been investigated, most commonly in a combinatorial approach given limited single-agent responses in the salvage setting.

Building on observations that phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signaling is commonly dysregulated in ALL, coupled with preclinical studies showing robust responses to mTOR inhibitors in animal models of human ALL,[5] Tasian *et al.* expanded the portfolio of mTOR inhibitor trials in pediatric relapsed ALL (Table 1), with the TACL 2014-001 phase I trial (NCT01614197) described in this issue of *Haematologica*. The mTOR inhibitor temsirolimus was administered in combination with cyclophosphamide and etoposide in pediatric patients 1-21 years of age with second or subsequent relapses or refractory B and T-cell ALL. Lessons learned from the prior Children's Oncology Group (COG) ADVL1114 phase I trial (NCT01403415) informed temsirolimus dosing and the chemotherapy platform. Treatment on COG ADVL1114 consisted of three weekly doses of temsirolimus in combination with UKALL R3 reinduction chemotherapy (vincristine, dexamethasone, pegaspargase and mitoxantrone). Seven of 15 patients (47%) achieved remission; however, the toxicity associated with temsirolimus in combination with asparaginase and steroids was excessive with dose-limiting toxicity at all dose levels despite two dose de-escalations of temsirolimus to 7.5 mg/m^2/dose.[6] The toxicity observed with a four-drug reinduction on COG ADVL1114 prompted the use of an alter-

Table 1. Early-phase mTOR inhibitor trials for relapsed pediatric acute lymphoblastic leukemia.

ClinicalTrials.gov identifier	Phase	Major findings	Treatment regimen	Population
NCT01523977 (10)	I	CR rate 86% Tolerable toxicity	Everolimus plus vincristine, prednisone, pegaspargase and doxorubicin	First relapse B- and T-ALL with CR1 >18 months
NCT01403415 (6)	I	CR/CRi rate 47% Excessive toxicity	Temsirolimus plus vincristine, dexamethasone, pegaspargase and mitoxantrone	Second or greater relapse B- and T-ALL
NCT01614197 (1)	I	ORR 49% Tolerable toxicity	Temsirolimus plus cyclophosphamide and etoposide	Second or greater relapse or refractory B- and T-ALL
NCT03328104	I	Ongoing	Everolimus plus nelarabine, cyclophosphamide and etoposide	First or greater relapse or refractory T-ALL
NCT03740334	I	Ongoing	Everolimus plus ribociclib and dexamethasone	Second or greater relapse or refractory B- and T-ALL

CR: complete response; CRi: complete response with incomplete count recovery; CR1: first complete remission; ALL: acute lymphoblastic leukemia; ORR: overall response rate.

native and historically more tolerable cyclophosphamide and etoposide chemotherapy platform on the TACL2014-001 trial and a reduction to two *versus* three doses of temsirolimus at a starting dose of 7.5 mg/m^2/dose.

Among the 15 evaluable T- and B-ALL patients, the addition of temsirolimus to the cyclophosphamide and etoposide backbone was safe and feasible in this heavily pretreated group, who had received a median of three (range, 2-7) prior salvage regimens and more than half of whom had undergone prior hematopoietic stem cell transplantation (HSCT). Only one patient experienced dose-limiting pneumonitis, pleural and pericardial effusions. Rates of fever and neutropenia, infectious toxicities and metabolic abnormalities were similar to those observed in other trials of cytotoxic therapy for relapsed ALL. There was a 47% overall response rate (complete, incomplete and partial responses) with 27% achieving a complete response and with responses at all four dose levels. Basal activation of the PI3K/mTOR signaling pathway inhibition with dose-dependent *in vivo* inhibition of phosphosignaling was observed in all patients who participated in these exploratory studies. Based on these data, the recommended phase II dose of temsirolimus in combination with cyclophosphamide and etoposide was deemed to be 15 mg/m^2/dose, the equivalent of the Food and Drug Administration-approved dose in adults, on days 1 and 8, although 25 mg/m^2 was tolerated and showed the greatest *in vivo* inhibition of PI3K pathway signaling.

One of the challenges in treating multiply relapsed ALL is prioritizing regimens. The expansion of immunotherapeutic options, particularly in B-ALL, raises questions regarding the role for small molecule therapy and optimal ways to deliver these agents in a growing treatment landscape. An important lesson from this trial is the benefit of using a tolerable platform when pursuing a combinatorial approach to reduce toxicity and optimize the delivery of targeted agents. Future options include combining mTOR inhibitors with other targeted therapies or immunotherapy. Studies have shown superior signaling phosphoprotein inhibition and antileukemia efficacy *in vivo* when PI3K/mTOR inhibitors are used in combination with tyrosine kinase inhibitors in models of Philadelphia chromosome-like ALL.[7] A clinical trial investigating everolimus in combination with the CDK4/6 inhibitor ribociclib (NCT03740334) is also underway based on encouraging preclinical data. Additionally, recent trials in adults have demonstrated the promise of combining small molecule inhibitors with immunotherapy, such as the bispecific CD19-directed antibody blinatumomab, although these approaches may require ongoing assessment of any potential impact of the targeted agents on T-cell function.[8,9]

Although the numbers are small, the responses in three of five patients with relapsed T-ALL on this trial is notable as there is a particularly urgent need for salvage regimens in T-ALL, for which there has been a paucity of effective treatment options relative to B-ALL. Another potential role for mTOR inhibitors is as a possible less toxic bridge to HSCT or chimeric antigen receptor T-cell therapy. In the multiply relapsed setting, in which achieving a minimal residual disease-negative complete remission can be challenging, mTOR inhibitors could have a potential role as part of a cytoreductive strategy, which could be followed by immunotherapy (e.g., chimeric antigen receptor T cells or blinatumomab/HSCT). Finally, this regimen is also an option following failure of HSCT or immunotherapy or in cases in which there is a lack of target antigen expression for available immunotherapies.

In summary, relapsed ALL remains a challenge and while newer treatments with immunotherapy, chimeric antigen receptor T cells, and advances in HSCT are improving outcomes, this is not without significant treatment-related toxicity and responses to salvage therapy remain unpredictable. Tasian *et al.* demonstrated that it is feasible to deliver an mTOR inhibitor in combination with chemotherapy and achieved responses in nearly half of a heavily pretreated patient population, presenting another option to consider as part of a strategy aimed at sustainable cure.

Disclosures

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Contributions

AP and ER contributed equally.

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