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Editorial Comment

Quest for effective agents to combat T-cell acute lymphoblastic leukemia

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Approximately 12–15% of childhood acute lymphoblastic leukemia (ALL) cases are classified as T-cell ALL and they generally have poorer prognosis than cases of B-cell precursor ALL. Not surprisingly, children with T-cell ALL in virtually all treatment centers are considered to have high-risk disease and receive appropriately intensified therapy. Although treatment outcome in newly diagnosed T-cell ALL has improved in several recent clinical trials [1,2], patients with relapsed disease continue to have dismal prognosis despite the use of allogeneic hematopoietic stem cell transplantation. A study by Kaspers and colleagues [3] in this issue of the *European Journal of Cancer* sought to find an explanation for the dire prognosis of relapsed T-cell ALL and to identify potentially useful drugs for this condition. By comparing the *in vitro* cellular drug resistance profiles between 30 patients with relapsed T-cell ALL and 121 with relapsed B-cell precursor ALL, the authors showed that recurrent leukemic T cells were more resistant to ifosfamide and cisplatin but more sensitive to thiopurines, leading them to suggest intensive use of thiopurines in patients with T-cell ALL in relapse.

The *in vitro* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium-bromide (MTT) drug-resistance assay has been shown by these investigators and others to have important prognostic implications, and has been used to select drugs for the treatment of specific subtypes of leukemia. More recently, it was used in studies to identify genes that are differentially expressed in ALL cells with resistance to prednisolone, vincristine, asparaginase and daunorubicin, and whose pattern of expression is related to treatment outcome [4].

The MTT assay and *in vitro* drug sensitivity tests in general have a number of limitations that affect their utility as clinical research tools. For example, the MTT assay cannot be used to test the sensitivity of cancer cells to methotrexate – one of the most commonly used antileukemic drugs – a restriction that prevented Kaspers and co-workers from assessing sensitivity to this agent in their analysis. The MTT assay also predicts that in newly diagnosed patients, leukemic T cells will be more resistant than leukemic B-cell precursors to virtually all chemotherapeutic agents, with the exception of epipodophyllotoxins and thiopurines, which in the assay were equally effective against both leukemic cell lineages [5]. However, in the current study, only ifosfamide and cisplatin, two drugs seldom used in the treatment of ALL, had significantly greater activity against relapsed B-cell precursor *versus* relapsed T-cell disease in the MTT assay. The investigators also found a more pronounced increase in drug resistance in relapsed B-cell precursor ALL than in relapsed T-cell ALL. These findings are difficult to reconcile with clinical observations establishing a much worse prognosis in patients with relapsed T-cell ALL as compared to relapsed B-cell precursor ALL. A possible explanation is that the authors failed to stratify their patients by time to relapse – a major prognostic variable in relapsed ALL.

It is still uncertain how one should apply the results of *in vitro* drug sensitivity testing in the clinical setting. As mentioned earlier, the MTT assay indicated that leukemic T cells in newly diagnosed patients are relatively resistant to virtually all antileukemic drugs, including

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asparaginase, but not to epipodophyllotoxins and thiopurines [5]. In another *in vitro* assay, leukemic T cells showed relative resistance to methotrexate because of reduced accumulation of methotrexate polyglutamates, due in part to the lower expression of folypolyglutamate synthetase, an enzyme that catalyses the formation of methotrexate polyglutamates [6]. Thus, one could argue for the intensive use of epipodophyllotoxins and thiopurines in the initial treatment of T-cell ALL, with limited use of other agents. The clinical reality is that neither drug alone (or in combination) has been shown convincingly to improve outcome in T-cell ALL. Rather, most of the therapeutic advances in this disease have come from intensive use of asparaginase and high-dose methotrexate (5 g/m^2) [1,7,8]. The inescapable conclusion is that increasing the dosages of drugs to which leukemic cells are relatively resistant is as likely to improve outcome as substituting agents shown to be effective by *in vitro* cytotoxicity assays. In this regard, it is doubtful that intensive use of thiopurines, especially mercaptopurine, which is used routinely during initial continuation treatment and has failed to salvage patients in previous clinical trials, would improve the outcome of relapsed T-cell ALL. Finally, arabinosylguanine, which has selective activity against T-cell malignancies [9], has yet to be tested with the MTT assay.

Ultimately, continued progress in the treatment of T-cell ALL will depend on the development of novel antileukemic agents targeted to molecules that are essential for maintenance of the transformed phenotype. Gene-expression profiling can separate cases of T-cell ALL into distinct subtypes based on common multistep oncogenic pathways; however, the prognostic significance of these subtypes may depend largely on the type of treatment administered [10]. A recent study provided evidence that a relative reduction in the level of SMAD3, an intermediate in the transforming growth factor-β tumor suppressor signaling pathway, promotes T-cell leukemogenesis in mice when coupled with loss of the p27^{kip1} protein [11], a finding suggesting that this pathway could be exploited with therapeutic intent. Another study identified *NUP214-ABL1* fusion transcripts in a subset of T-cell cases with extrachromosomal (episomal) amplification of the *ABL1* gene [12,13]; subsequent demonstration that this constitutively phosphorylated tyrosine kinase is sensitive to imatinib suggests a new therapeutic approach to this subset of T-cell ALL cases. Most interesting perhaps, is the discovery of mutations in *NOTCH1*, a gene encoding a transmembrane receptor that regulates normal T-cell development, in more than 50% of T-cell ALL cases [14]. Because the transcriptional stimulatory effects of the mutant, NOTCH1 protein could be completely abrogated by a γ-secretase inhibitor [14], the authors have undertaken a phase I/II clinical trial of this agent, which is also being considered for the treatment of Alzheimer's disease. It may be important in this regard that a potent γ-secretase inhibitor (LY-411,575) blocked T-cell precursor differentiation in transgenic mice [15]. Alternatively, one might obtain equivalent results by substituting inhibitors of the ubiquitin/proteasome system that affect other proteins in the NOTCH signaling pathway [16]. Although as many as 75% of T-cell ALL patients are cured with intensive chemotherapy, new strategies are needed for patients with refractory or relapsed disease. Targeted treatments that interfere with T-cell transformation pathways appear to hold the greatest promise for advancing cure rates in this disease.

Conflict of interest statement

None declared.

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