the heart is affected, then the prognosis is dismal. Actually, patients presenting with clinically evident heart failure and elevated cardiobiomarkers have a median survival of just a few months. With current treatments, there is often not enough time for any active therapy to reverse the clinical course.

Yet the plasma cells that produce amyloidogenic light chain may have an Achilles' heel. Preclinical data indicate that misfolded amyloidogenic light chains increase the load that the quality control system within the plasma cell has to cope with and induce endoplasmic reticulum (ER) stress. The plasma cell is dependent on the integrity of the mechanism for the degradation of these proteins to retain intracellular homeostasis, and proteasome is central to the maintenance of this equilibrium.[5] Blocking proteasomal degradation of proteins increases ER stress and results in cell apoptosis. Plasma cells that are producing larger amounts of immunoglobulins may be more vulnerable to the proapoptotic effect of proteasome inhibition.[6] Bortezomib targets the activity of the proteasome and thus leads vulnerable plasma cells to apoptosis (see figure). A proof of concept for the activity of bortezomib in AL amyloidosis came a few years ago from 2 small series.[7,8] The results were encouraging: bortezomib was not only active but also a fast-acting agent, even in pretreated patients. A prospective phase 1 study confirmed that bortezomib either on a twice-weekly or weekly schedule was active and safe in patients with relapsed AL[9] and a retrospective analysis from 3 European centers highlighted the efficacy of bortezomib with or without dexamethasone.[10] Notably, the results in previously untreated patients were very promising. In the current prospective phase 2 study by Reece et al we move another step forward: single-agent bortezomib either using a weekly or a twice-weekly schedule resulted in hematologic response rates of 68.8% and 66.7%, respectively, including 37.5% and 24.2% complete responses.[1] Importantly, median time to first response for the twice-weekly schedule was just 1 cycle of single-agent bortezomib. Moreover, the responses were durable: $>75\%$ of patients had response durations of ≥ 1 year in either schedule. Organ responses were also significant, especially accounting for the long-standing amyloidotic involvement in patients with relapsed AL and included 29% renal and 13% cardiac responses. However, toxicity with bortezomib in patients with AL is not negligible. Considering that most patients with AL have multiorgan dysfunction and may be quite frail, treatment with bortezomib should be carefully monitored. Fortunately, this article by Reece et al provides some guidance: a weekly schedule may be a less toxic but active regimen, although response may take somewhat longer than with the twice-weekly schedule.[1] Nevertheless, the study did not include patients with more advanced cardiac disease, such as those with New York Heart Association class III or IV, which carry the poorest prognosis. In these high-risk patients, the results may not be as impressive,[11] probably because organ failure predetermines the outcome.

Definitely bortezomib has the highest activity that has ever been recorded for a single agent in AL amyloidosis. The current study by Reece et al provides practice-changing data and shows the path we should follow. Bortezomib should be introduced in earlier phases of the disease: upfront bortezomib-based therapies should be the next step and we should proceed quickly. Furthermore, combination of bortezomib with dexamethasone and with an alkylating agent is likely to further enhance both hematologic and organ responses. Given the rarity of the disease, this study also shows how to move: collaborative, multinational, multicenter design is the only way to move rapidly, with well-designed phase 2 and 3 studies. AL amyloidosis is an orphan disease, and our patients have no time to spend waiting for the results of slowly accruing studies. We owe it to our patients to develop more active treatments as soon as possible.

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● ● ● CLINICAL TRIALS

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Childhood T-ALL: it's time to move on

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The results of a randomized trial of high-dose methotrexate (HD MTX) in childhood T-cell ALL (T-ALL) reported by Asselin et al on behalf of the Children's Oncology Group (COG) in this month's issue of *Blood* demonstrate both the promise and the challenge of further improving the outcomes of children with high-risk ALL through intensified application of conventional chemotherapeutic agents.[1]

Recent nonrandomized studies in childhood T-ALL report an ~ 70% to 75% 5-year event-free survival (EFS).[2-5] The trial reported by Asselin and colleagues, POG 9404, confirms a previous nonrandomized report of the benefit of HD MTX in this high-risk group

of patients.[2] In POG 9404, children with newly diagnosed T-ALL or non-Hodgkin lymphoma (NHL) were randomized to receive 4 doses of 5 g/m^2 of HD MTX as a 24-hour infusion in the context of a modified intensive Dana-Farber Cancer Institute (DFCI) regimen.[3] The benefits of HD MTX were substantial enough to warrant early closure of the randomization. That's the good news.

The not-so-good news: outcome on the HD MTX arm of POG 9404 was no better than other T-ALL regimens. The results of the POG 9404 trial demonstrate that even seemingly minor modifications to a treatment plan can significantly impact outcome. While POG 9404 closely mirrored the DFCI 87-01 regimen, modifications, including a delay in the introduction of prophylactic cranial irradiation (CXRT) and a reduction in the intensity of early intrathecal chemotherapy, were made in an effort to minimize the risk of treatment-related neurotoxicity. These changes likely contributed to a higher rate of CNS-involved relapses, many of which occurred during the first 6 months of treatment, on the POG study compared with the DFCI regimen on which it was based. For T-ALL patients treated without HD MTX on the modified control arm of the POG protocol, the overall outcome (5-year EFS of 68%) was lower than expected, while the outcome of the HD MTX arm (5-year EFS of 79%) was similar to those of other childhood T-ALL trials. Thus, the addition of HD MTX, while associated with an improvement in outcomes in those who received it compared with those who did not, did not provide a survival advantage compared with the original DFCI regimen.

So one lesson of POG 9404 is that the addition of HD MTX may allow CXRT to be delayed in patients with T-ALL without a negative impact on EFS. What we did not learn is whether the addition of HD MTX would allow CXRT to be eliminated altogether. In the trial reported by Asselin et al, as in previous BFM and DFCI trials, T-ALL patients received prophylactic CXRT. Current protocols typically use a lower dose (12 Gy instead of 18 Gy), but CXRT is still administered to the majority of patients with T-ALL on most treatment regimens. Recently, other groups have reported similar EFS results for patients with T-ALL treated without CXRT using 4 doses of postremission HD MTX and additional doses of intrathecal chemotherapy.[4,5] This strategy may be successful for some patients with T-ALL, although in general T-ALL patients treated without CXRT have a higher risk of CNS-involved relapses compared with similarly treated B-precursor patients, and for some T-ALL patients (eg, those with high-presenting leukocyte counts or CNS-3 status at diagnosis), relapse risk may exceed rates observed in trials using CXRT.[4] In addition, sequelae of the various CNS-directed therapies in this population remains to be elucidated. Whether or not CXRT and/or HD MTX are used, the bottom line is that 20% to 25% of children with T-ALL treated with current regimens experience a relapse, and salvage after relapse remains dismal. While sorting out which subsets of patients may avoid CXRT, we need to focus on strategies to improve cure rates. Achieving this goal will require novel approaches involving more effective T-ALL–specific drugs and better prognostic factors to identify T-ALL patients who are not cured by currently available therapies.

Nelarabine, a synthetic deoxyguanosine derivative that is arguably the most promising new drug for T-ALL to emerge in more than a quarter of a century,[6] is currently undergoing evaluation in a randomized COG study (AALL0434) of children with newly diagnosed T-ALL. Despite its significant efficacy in recurrent T-cell disease, nelarabine has been associated with substantial neurotoxicity in the relapse setting, leading to reservations about its widespread use in newly diagnosed patients. The identification of abnormalities in the Notch pathway[7] holds the promise of new therapeutic strategies, such as γ secretase inhibition. Although early attempts to introduce such interventions have not translated into therapeutic benefit for patients with T-ALL,[8] a number of new compounds with strong preclinical rationale and activity are now entering clinical evaluation.

In addition to new drugs, we need better prognostic factors to identify those patients most in need of more effective therapies. On the POG 9404 trial, age ≥ 10 years, high white blood cell count, and male sex were adverse prognostic factors. Other studies have not confirmed these results. The use of minimal residual disease assessments to tailor postremission therapy for patients with T-ALL is currently under investigation. A distinct subset of childhood T-ALL, termed early precursor T-cell ALL (ETP),[9] has been associated with an especially poor outcome, and, if prospectively validated as an independent prognostic factor, may help to identify patients at diagnosis who would benefit from alternative treatment approaches.

In summary, the report by Asselin and colleagues confirms the activity of HD MTX in newly diagnosed childhood T-ALL, while also demonstrating that reductions in the intensity of CNS-directed therapy may dilute its therapeutic benefit. How, when, and in what therapeutic context to best apply HD MTX in this population remains unclear. Other strategies to optimize the use of standard antileukemic agents, such as the postinduction intensification of asparaginase,[3] may also be beneficial. However, for children with high-risk T-ALL (such as ETP-ALL) and those with recurrent disease, improvement in outcome will require the introduction of new agents targeting critical pathways in T-ALL leukemogenesis, chemotherapy-resistant leukemia-initiating cells,[10] or both. Rearranging the deck chairs on the Titanic will not benefit children with ETP-ALL; it is time to move on to the evaluation of molecularly targeted therapies in childhood T-ALL.

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