Tmax was 1 hour), with a dose–proportional increase in plasma exposure. Pharmacodynamic studies in both trials indicated a dose-dependent increase in whole blood 20S proteasome inhibition. The safety profile of ixazomib was favorable. With weekly dosing, drug-related grade ≥3 AEs were seen in 53% of the 60 patients treated, including thrombocytopenia (33%), neutropenia (18%), diarrhea (17%), and fatigue (8%).1 Thrombocytopenia appeared transient and cyclical. Of note, only 1 case of grade 3 PN was observed. With biweekly dosing, the most common drug-related grade ≥3 AEs overall in 60 treated patients were similar, including thrombocytopenia (37%), neutropenia (17%), skin rash (8%), and fatigue (7%).2 Interestingly, no grade 3 PN was reported. Disease response was also promising. Using weekly dosing, 8 of 30 (27%) response-eligible patients treated at the MTD achieved a partial response.1 The median duration of response was 7.3 months. Of note, patients had received a median of 6 prior regimens, and nearly three quarters of them were refractory to their last prior therapy. With the biweekly regimen, 15% of 55 response-eligible patients achieved PR or better, with 76% reaching at least stable disease, and 18% of the patients remained on treatment of ≥12 cycles.3 Patients had previously received a median of 4 prior lines of therapy, and 60% were refractory to their last prior therapy. The reports of these 2 trials present the first in the literature of the investigational oral PI ixazomib. They provide important findings on the safety profile of the agent demonstrating that AEs were manageable with supportive care measures and dose reductions. Almost no occurrence of grade 3 PN was seen. In addition, clinically meaningful responses were seen. Certainly, we have to be cautious when comparing data collected on a total of 120 patients enrolled in 2 phase 1 trials1,2 vs data collected on hundreds of patients treated with bortezomib and carfilzomib. Nevertheless, the strong efficacy signal combined with a favorable toxicity profile indicates that ixazomib could be the PI of choice in the future. With improving survival in MM, attention is increasingly focusing on the ease of administration of novel agents, and the oral route of administration of ixazomib is a crucial point for our patients. The results of these 2 phase 1 trials also suggest that a once-a-week administration could be the optimal schedule. Based on population pharmacokinetic analysis, the 2.97 mg/m² MTD of the weekly dosing can be converted into a fixed-dose equivalent of 4.0 mg, which will allow the implementation of simple dose reductions if needed.10 In vitro and in vivo data strongly support the use of combinations of PI with immunomodulatory drugs and steroids. The triplet all-or combination of ixazomib-lenalidomide-dexamethasone could be the most convenient and effective in the near future.11 Ongoing randomized, double-blind, multicenter studies that are investigating weekly dosing of ixazomib 4.0 mg (vs placebo) plus lenalidomide-dexamethasone in relapsed/refractory MM patients (#NCT01564537) and in previously untreated transplant-ineligible MM patients (#NCT01850524) will address this important question.

Conflict-of-interest disclosure: P.M. is on the advisory boards for Millennium-Takeda, Janssen, and Onyx. ■

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CLINICAL TRIALS & OBSERVATIONS

Comment on O’Connor et al, page 1056

First do no harm: infectious deaths in pediatric ALL

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In this issue of Blood, O’Connor and colleagues describe infection-related mortality on the United Kingdom Childhood Acute Lymphoblastic Leukaemia Randomised Trial 2003 (UKALL 2003) for children with newly diagnosed acute lymphoblastic leukemia, reporting a 5-year cumulative incidence of 2.4%, with Down syndrome (DS) being the factor most predictive of increased risk.1 Overall survival in childhood ALL has steadily improved during the last several decades, to a current rate of more than 90%.2-4 These dramatic gains in survival, largely attributable to lower relapse rates, have been accompanied by increasing attention to the importance of reducing treatment-related mortality (TRM), which is mainly a result of infectious causes. For intermediate- and high-risk ALL, the progressive intensification of chemotherapy on modern ALL treatment regimens has reduced relapses, but with the
Timing of IRM in DS and non-DS patients (*P < .048). See Figure 2A in the article by O’Connor et al that begins on page 1056.

unavoidable consequence of a greater risk for TRM. For low-risk ALL, TRM is also a concern, as outstanding survival rates mean the number of deaths caused by TRM now equals the number of deaths resulting from relapse. The highly intensive regimens required for treatment of pediatric acute myeloid leukemia have generated attention to the study of TRM, but investigations of similar scale and depth are lacking in ALL. Data from large cooperative group trials such as the present study are important to characterize the problem and suggest approaches to reduce it.

O’Connor and colleagues report on the largest infection-related mortality (IRM) cohort in pediatric ALL to date, a retrospective analysis of UKALL 2003, a recently completed trial for the treatment of newly diagnosed ALL in children aged 1 to 24 years, which accrued 3126 subjects between 2003 and 2011. Patients were stratified to standard-, intermediate-, or high-risk treatment on the basis of clinical features at presentation, cytogenetics, and response to induction therapy. In total, there were 75 cases of IRM, which constituted 2.4% of the eligible patients, 30.1% of the 249 deaths overall, and 64% of the 117 treatment-related deaths. DS was the factor most significantly associated with IRM, with an odds ratio of 12.08, followed by higher-intensity treatment regimen and National Cancer Institute high-risk status (age at diagnosis >10 years and/or initial white blood count >50 x 10⁹/L). In terms of timing, IRM occurred more often during induction than during any other treatment phase in the cohort overall. Of note, however, IRM in children with DS was more evenly distributed across all treatment phases, with a significantly higher percentage of events occurring during maintenance than for non-DS children (37.5% vs 15.2%; P = .048; see figure). This persistent vulnerability of children with DS to IRM throughout all treatment phases, including maintenance, was also observed in a recent large, retrospective analysis of DS-ALL patients enrolled on multiple international trials, suggesting it is not limited to a specific treatment regimen.

The O’Connor study is significant because it establishes solid benchmark data in the largest cohort to date regarding frequency, timing, organisms, and risk factors for IRM. The study has distinct implications for DS and non-DS patients, given the significant differences in frequency and timing of IRM between the 2 groups.

Regarding management of non-DS patients, key points include the heightened risk for IRM during induction and other intensive phases of treatment, the predominance of respiratory and catheter-associated bloodstream infections, and the occurrence of death within 48 hours of initial presentation in 55% of the IRM cases. These findings highlight the critical importance of vigilance by families and providers during intensive phases of therapy, meticulous care of central venous catheters, and rapid, aggressive management of infections. As the authors point out, their study also highlights the need for further investigations to both characterize and reduce IRM in ALL. Our current portrait of IRM is limited by difficulties comparing studies because of varying definitions of key measures such as invasive fungal infections and catheter-associated bloodstream infections. It is also limited by the scope of data captured, which often lacks information about risk factors such as neutropenia, body mass index, hyperglycemia, and other comorbidities. Finally, data are lacking on how best to combat IRM. There is no current intergroup consensus on front-line treatment of ALL regarding the role of supportive measures such as IgG replacement and antibiotic and antifungal prophylaxis, or the risk-benefit ratio of treatment components such as monthly steroid pulses and an extra year of maintenance therapy for boys. Several ongoing cooperative group studies may provide answers to these questions in the future.

Regarding management of DS patients, the 12-fold increased risk for IRM drew attention during the conduct of the UKALL 2003 trial, and an amendment in 2009 implemented numerous modifications to treatment and supportive care. Similar unacceptably high IRM was also observed around this time on the Children’s Oncology Group (COG) standard-risk and high-risk trials, and safety amendments to these trials were also implemented. These modifications reduced subsequent induction mortality on UKALL 2003 and the COG standard-risk trial, although further events on the COG high-risk trial led to its eventual closure to patients with DS. The largely improved outcomes after these safety amendments are encouraging, but further follow-up and analysis are needed to determine whether these modifications result in an overall reduction in IRM for children with DS-ALL, and if so, whether this occurred without a corresponding increase in the risk for relapse. Because children with DS-ALL have shown an increased risk for relapse as well as IRM on several recent protocols, any treatment modifications to mitigate IRM must be carefully designed in consideration of the competing risk for disease relapse.

Introduction of targeted therapies with relatively low systemic toxicity, such as
Janus kinase inhibitors, based on the unique molecular features of DS-ALL, is an avenue that may eventually enable safe reductions in conventional chemotherapy.10

As survival has improved in pediatric ALL, the need for efforts to reduce IRM is clear. This work by O’Connor and colleagues is a valuable contribution to the field, demonstrating the importance of capturing well-defined toxicity data on large cooperative group trials and identifying important aspects of IRM that will guide future efforts to more effectively prevent and treat infections during the treatment of ALL.

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**LYMPHOID NEOPLASIA**

Comment on Wang et al, page 1089

Old and new news in CLL: “It’s the pathway, stupid!”

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In this issue of Blood, Wang et al demonstrate how mutations in the Wnt/β-catenin pathway in chronic lymphocytic leukemia (CLL) lead to activation of this pathway.1 The work presented demonstrates that this pathway is likely to contribute to CLL pathogenesis, at least in a subset of patients, and suggests that it may contain potential therapeutic targets. These observations are following the authors’ groundbreaking work on the genetic landscape in CLL2,3 and by using exciting, novel transfection technology (ie, silicon nanowires).4 Thus, the notoriously difficult-to-transfect CLL cells could be modified to be able to target a pathway that has been identified by indirect evidence from next generation sequencing, demonstrating that attacking the mutated proteins by genetic modification is feasible. Indeed, at least for some proteins tested, modification of the pathway on a number of levels led to changes in CLL behavior consistent with a role of the Wnt/β-catenin pathway in CLL pathogenesis. The paper must be read to fully appreciate the elegance of the approaches taken, as well as understand the potential limitations of the approach.

The paper has impact beyond CLL that is worth exploring. First, the authors attack a recurrent problem, observed during the recent explosion of genetic knowledge on tumorigenesis. Massively parallel sequencing approaches suggest that certain mutations in tumors act as so-called “drivers” largely using a “guilt-by-association” approach. The logic is that recurrent mutations selected by independent tumor evolution pathways must be important. If the mutation can be also placed into the context of a plausible oncogenic pathway, then we tend to believe that we have, indeed, found the culprits. We commend Wang et al! for taking their own observations from genetics to a cell biology platform and their attempts to move a step closer to elucidating not just the association, but the action of the mutations they described earlier.

Of course, such approaches have been taken in the past, but mainly for a limited type of lesion, leading to the second point. We, as hematologists (I cannot speak for all hematologists, but as a figure of speech, allow me to say) have been raised on simple tumor biology models, not the least because it was in hematology, where some of the first insights into molecular oncogenesis were developed. Single and highly recurrent lesions, such as the Bcr-Abl or PML-RARA translocations (or more recently B-Raf mutations) were identified, validated in cell biology and animal models to the point where it was possible to stringently identify culprits, fulfilling Koch’s postulates, and targeted treatment could be initiated effectively. This enormous success story may have biased our views and expectations in many malignancies, until the arrival of next-generation sequencing and the confusing complexity we have “endured” since then. Enter CLL! CLL seems a very particular beast in that is a prototypically odd malignancy for a number of reasons. First, it shows an intricate interaction and dependency on multiple microenvironmental cues (see the review by Burger5), suggesting that not all transforming “events” need to be hardwired by mutations in the leukemic clone itself.

Indeed, CLL induces signaling in its microenvironment that seems essential for its survival.6 Second, with the possible exception of deletion 13q, no real high frequency transforming events have been defined yet. Indeed, the genetic landscape, as previously demonstrated by the authors of this paper in discussion, looks extraordinarily “colorful.”7,8 The important achievement of the Dana Farber group was to use a bioinformatic pattern...
First do no harm: infectious deaths in pediatric ALL

Karen R. Rabin