exocytosis, and in particular Rab27a function, in the process of extracellular bacterial killing by neutrophils.

Both the lung epithelium and the immune cells contribute to effective clearance of bacterial infection in CF patients. It has been shown that ivacaftor treatment improves lung function in CF patients compared with placebo. However, this study provides some critical novel evidence of how mutations of the CFTR channel affects neutrophils key functional responses compromising their antimicrobial capacity and the molecular mechanisms of how ivacator might correct the CFTR channel abnormalities and benefit patients with CF.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Comment on Kumar et al, page 1047, and on Richardson et al, page 1038

Oral therapy for multiple myeloma: ixazomib arriving soon

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In this issue of Blood, Kumar et al and Richardson et al report the results of 2 phase 1 trials that investigated 2 different administration schedules of ixazomib in patients with relapsed/refractory multiple myeloma (MM): weekly and biweekly dosing. Kumar et al determined that the maximum tolerated dose (MTD) of single-agent oral ixazomib given weekly for 3 of 4 weeks was 2.97 mg/m². Detailed pharmacokinetic analyses showed that after multiple dosing, the terminal half-life was long (3.6-11.3 days), supporting once-weekly dosing. In the trial by Richardson et al, the MTD of single-agent, oral ixazomib, given on days 1, 4, 8, 11 of a 21-day cycle was found to be 2 mg/m².

Two proteasome inhibitors (PI), bortezomib and carfilzomib, are currently approved for the treatment of myeloma; ixazomib is expected to be the first oral PI available in the near future.

Proteasome inhibition has emerged as an important therapeutic strategy in MM. Bortezomib was the first-in-class PI to be introduced into the clinic. It is a dipeptidyl boronic acid–based specific, reversible PI that targets the chymotrypsin– and caspase–like active sites of the 20S proteasome, with minimal effect on trypsin–like activity. By inhibiting the proteasome, bortezomib acts through multiple mechanisms, suppressing tumor survival, and arresting tumor growth, spread, and angiogenesis. Since the publication of the first phase 1 trials of bortezomib 12 years ago, this drug has contributed substantially to the observed improvement in survival in MM patients over the last decade. First approved as an intravenous (IV) single agent in the relapsed setting, bortezomib is now predominantly used in combination regimens and is an integral part of front-line therapy. The standard twice-weekly schedule may be replaced by weekly infusion, especially when bortezomib is used as part of combination regimens. Additionally, a new route of bortezomib administration, subcutaneous (SC) infusion, was recently approved. The most common bortezomib-associated toxicities are gastrointestinal symptoms, anemia, thrombocytopenia, fatigue, and peripheral neuropathy (PN). Neurotoxicity remains the most cumbersome adverse effect; however, it can be managed and limited with dose modification, weekly dosing, and by SC administration.

Carfilzomib is an irreversible PI that belongs to the epoxyketone class and is structurally and mechanistically distinct from bortezomib. This second-in-class PI demonstrates potent and sustained inhibition of the chymotrypsin–like activity of the proteasome with a greater selectivity for the chymotrypsin–like protease compared with bortezomib and lower affinity for the trypsin– and caspase–like proteases. Single-agent IV carfilzomib has produced robust and durable responses in clinical trials, and it has been approved in the United States for the treatment of relapsed and refractory MM. Due to its favorable safety profile, carfilzomib is an attractive agent for use in combination strategies. Ongoing pivotal randomized phase 3 studies are exploring the efficacy and safety of carfilzomib combinations in patients with relapsed MM and in transplant-eligible patients. Adverse events (AEs) related to IV carfilzomib are manageable. The most common serious AEs are pneumonia, acute renal failure, fever, and congestive heart failure. Infusion reactions to carfilzomib can be reduced by pretreatment with dexamethasone and IV fluids. Importantly, the PN commonly observed with bortezomib is less severe and less frequent with carfilzomib.

MLN9708, ixazomib, is another boronate PI that is a reversible inhibitor of primarily the chymotrypsin–like activity of the 20S proteasome. However, in contrast to bortezomib, ixazomib has a shorter dissociation half-life, and in preclinical studies, it demonstrated greater tissue penetration compared with bortezomib. Most importantly, ixazomib is orally available.

Pharmacokinetic examinations confirmed that ixazomib was rapidly absorbed (median
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-evaluable 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-evaluable 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 PIs with immunomodulatory drugs and steroids. The triplet oral 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.

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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
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