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CLINICAL TRIALS AND OBSERVATIONS

Comment on Larocca et al, page 3027

Addition by subtraction

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In this issue of *Blood*, Larocca and colleagues show for the first time that selected elderly patients with newly diagnosed multiple myeloma benefit from modification of standard myeloma treatment based on their level of frailty, which results in lower toxicity while preserving efficacy.[1]

The authors selected patients who were intermediate-fit based on the International Myeloma Working Group (IMWG) frailty index. In 2015, the IMWG developed a score that included age, dependence, and comorbidities.[2] The Katz Activity of Daily Living (ADL) and the Lawton Instrumental Activity of Daily Living (IADL) were used to assess dependence because of physical and/or cognitive impairment. Comorbidities were defined using the Charlson Comorbidity Index. Three groups were identified: fit, intermediate-fit, and frail. The IMWG frailty score is prognostic for mortality and nonhematologic toxicity and has been extensively externally validated, but until now, data supporting its use for treatment modifications were lacking.

Larocca et al are the first group to investigate treatment modification in intermediate-fit patients in a randomized clinical trial. Participants in the standard-treatment arm received standard-dose lenalidomide (25 mg)–dexamethasone (Rd) until progression. In the investigational arm, after 9 Rd induction cycles, the lenalidomide dose was tapered to 10 mg and dexamethasone was discontinued (Rd-R). These dose and schedule adjustments improved event-free survival (EFS).

These results are important for clinical practice and for designing future clinical trials. First, the authors are to be congratulated for completing this investigator-initiated academic trial, which is becoming an increasingly difficult thing to do in the tightly regulated clinical trial field, which prioritizes trials focused on regulatory approval and treatment intensification.[3] Although further intensification and innovations in multiple-drug regimens are needed to advance the field, more intensive therapy might not benefit vulnerable older patients who are at increased risk for treatment toxicity and poor survival.[4] This population will grow, given the current median age at diagnosis of 70 years and increasing longevity.

The authors lay the foundation for high-quality evidence-based regimens that lower toxicity while preserving efficacy. Guidelines for treating older adults previously relied on expert consensus opinion, because data regarding dose modifications are scarce. High-dose dexamethasone reduces overall survival (OS) compared with lower-dose dexamethasone; thus, dexamethasone 40 mg per week became standard of care. In patients who were not eligible for transplantation, dexamethasone-based regimens caused high rates of infections, diabetes (made the disease worse in those who already had diabetes), and gastrointestinal and psychiatric complications. Therefore, in patients age ≥75 years, a lower weekly dose of 20 mg dexamethasone was advised.[5,6] It was unknown whether dexamethasone could be discontinued without reducing progression-free survival (PFS) and OS. Now, the results of the Larocca et al study show that intermediate-fit patients can safely discontinue dexamethasone after induction therapy.

The investigators selected EFS as a combined primary end point, reflecting both efficacy and toxicity. Such composite end points are essential for guiding treatment in vulnerable patients. Indeed, EFS was superior with Rd-R, whereas PFS and OS were not. This was mainly the result of a lower incidence of grade ≥3 nonhematologic toxicity (31% vs 40%). EFS is an important acknowledgment that older adults often prioritize outcomes other than disease control or survival; 58% of older adults with cancer reported that they would rather live a shorter period of time than lose their independence (ie, require assistance with IADLs or ADLs), and a full 80% prioritized maintaining their cognition over length of survival.[7]

However, several questions remain. How lenalidomide dose modification and dexamethasone discontinuation contributed to improvement of EFS cannot be explained exactly, because the EFS curves started to diverge during the first 9 months of therapy when treatment was similar in both arms. It might be that more patients in the Rd group discontinued lenalidomide during the first 9 cycles, which is supported by the fact that both the median duration of lenalidomide therapy and the lower limit of the interquartile range were shorter: 12.8 vs 17.3 months and 4.5 vs 7.2 months, respectively. For future studies, it may be appropriate to randomly assign patients after induction therapy or blind participants and clinicians to randomization until induction is complete.

Second, daratumumab-Rd (Dara-Rd) may supplant Rd as a preferred first-line regimen in patients who are not eligible for transplantation, given its projected median PFS of >50 months vs 34 months with Rd in the MAIA trial. Toxicity of daratumumab is minimal with limited infusion-related toxicity, which suggests that it will be well-tolerated in intermediate-fit and frail patients.[6] Although 40% of patients were older than age 75 years, the patient

population in the MAIA trial differed from that in the trial by Larocca et al; the median PFS was 34 months in the MAIA trial vs 20 months in the Larocca et al trial. Moreover, infections were 1.5 times higher with Dara-Rd vs Rd. Therefore, the results of trials investigating daratumumab in intermediate-fit and frail patients are eagerly awaited.[8]

The Larocca study was not powered to perform subgroup analyses based on whether the patient was intermediate-fit due to age only or due to geriatric impairments. Preliminary data suggest that outcomes are worse in the presence of comorbidities and/or geriatric impairments.[8] Although the IMWG frailty score is an excellent initial foray into stratifying older patients based on aging-associated vulnerabilities, further characterization of impairments generally not assessed in older adults with myeloma such as cognition, psychological status, and objective physical performance (eg, gait speed) may further improve risk stratification in older adults.[9]

Finally, in future trials, investigators studying older adults may extend beyond EFS to other novel composite outcomes with even greater patient centeredness. One such novel composite end point, overall treatment utility, was designed to reflect patient and clinician perspectives and incorporate subjective and objective measures to determine whether the treatment, overall, had been worthwhile.[10]

In summary, for the first time Larocca et al provide evidence for frailty-adapted treatment in intermediate-fit patients. After induction, the dose of lenalidomide may be tapered and dexamethasone may be discontinued, resulting in higher cumulative doses of lenalidomide and lower toxicity without negatively impacting survival. Although data were not presented on quality of life, it stands to reason that subtracting dexamethasone after induction adds to a patient's quality of life. To implement frailty-adjusted dosing on a large scale in general practice, there is a need to prospectively investigate newer treatment regimens, especially novel immunotherapies, and to examine further refinements in geriatric assessment, which will enable identification of subgroups of intermediate-fit and frail patients, as we aim to provide personalized treatment to each of our elderly patients with myeloma.

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LYMPHOID NEOPLASIA

Comment on Kennedy et al, page 3064

Revisiting TLR9 as a target for CLL therapy

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In this issue of *Blood*, Kennedy et al[1] describe a Toll-like receptor 9 (TLR9)-driven mechanism of therapeutic escape/evasion in patients with chronic lymphocytic leukemia (CLL), mediated by synergistic survival signaling via nuclear factor (NF)-κB and STAT3. These findings suggest a potential CLL treatment strategy using combined targeting of TLR9 and Bruton's tyrosine kinase (BTK).

CLL is one of the most common adult leukemias, and the incidence and prevalence of CLL is increasing. Therapeutic options for CLL patients have expanded in recent years providing for more personalized regimens using targeted agents, such as inhibitors of BTK, phosphatidylinositol 3-kinase δ/γ, or B-cell lymphoma 2 signaling downstream from B-cell receptor (BCR). Despite these advances, must unmutated CLL (U-CLL) remains incurable except for allogenic stem cell transplantation.[2] Beyond BCR signaling, TLR9 has been long recognized for contributing to CLL cell activity. TLR9 is an innate immune receptor and an endosomal sensor of pathogenic DNA or mitochondrial DNA released from dying cells. Synthetic TLR9 agonists, such as oligodeoxynucleotides containing unmethylated