COUNTERPOINTS

Current Controversies in Hematology and Oncology

What Should Standard Frontline Therapy Be in Older Patients With Chronic Lymphocytic Leukemia?

Now that ibrutinib (Imbruvica, Pharmacyclics/Janssen), a Bruton's tyrosine kinase inhibitor, has been approved for use in the frontline setting for patients with chronic lymphocytic leukemia (CLL), should it become standard treatment for patients older than 60 years? Or are proven chemoimmunotherapy regimens still best for these patients? Here, Dr Jennifer A. Woyach makes the case for ibrutinib in older patients, whereas Dr Clemens-Martin Wendtner argues in favor of chemoimmunotherapy.

Ibrutinib Should Be Standard Frontline Therapy

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The development of small molecules that target the B-cell receptor signaling pathway heralded a paradigm shift away from chemoimmunotherapy for patients with relapsed CLL. With the recent US Food and Drug Administration approval of ibrutinib in the frontline setting, the same shift is poised to occur for patients with treatment-naive disease. Ibrutinib should be considered standard frontline therapy for older patients and those with significant comorbidities. Although the definition of "older" is subject to debate, here, we will consider older patients to be those past the age of 60 years.

Until recently, few studies had looked specifically at initial therapy for older patients with CLL. Although chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen Idec; FCR) is standard for younger patients who have CLL, limited analysis of outcomes in patients 70 years of age and older demonstrated lower response rates and increased toxicity.[1] Similarly, the prospective German CLL Study Group (GCLLSG) CLL5 trial (Fludarabine or Chlorambucil as First-Line Therapy in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia), which examined fludarabine vs chlorambucil as single agents in patients 65 years of age and older, showed no differences between them in regard to progression-free survival (PFS)

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Chemoimmunotherapy Should Be Standard Frontline Therapy

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Although the advances made in the treatment of CLL in recent years have been amazing, a cure remains elusive for the majority of patients. This is especially true for patients with CLL who are older than 60 years; they usually are not candidates for an allogeneic transplant, which is the only curative intervention for CLL. Thanks to the many cooperative groups around the world that have carefully conducted clinical trials, however, we now know that we can significantly prolong life expectancy in certain well-defined subgroups of patients with CLL. Despite impressive results—mostly in the relapsed setting—with novel agents that interfere with B-cell receptor signaling, such as ibrutinib and idelalisib (Zydelig, Gilead), chemoimmunotherapy remains a solid and well-tested standard for patients with CLL in the frontline setting.

The majority of patients with CLL who are older than 60 years are not physically fit and have one or more comorbidities. We should not forget, however, that an increasing number of athletic and fit patients with CLL who are older than 60 years do exist and can benefit from an aggressive FCR regimen. Based on data from the GCLLSG CLL10 trial (FCR or BR in Patients With Previously Untreated B-Cell Chronic Lymphocytic Leukemia), FCR is recommended for physically fit patients up

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and overall survival (OS), despite a superior overall response rate for fludarabine.[2] Retrospective analysis of the Cancer and Leukemia Group B (CALGB) studies also showed no advantage of fludarabine over chlorambucil in the elderly population, but it did show improvements in PFS and OS with the addition of rituximab in both younger and older patients.[3] More recently, the GCLLSG CLL11 trial (A Study of Obinutuzumab [RO5072759 (GA101)] With Chlorambucil in Patients With Previously Untreated Chronic Lymphocytic Leukemia [Stage 1a]) showed the efficacy of chlorambucil and obinutuzumab (Gazyva, Genentech) in a predominantly older population, with a median PFS of 29.2 months.[4] The GCLLSG has also investigated bendamustine and rituximab (BR) as frontline therapy, and a phase 2 study of this combination showed a median event-free survival of 33.9 months and an OS of 90.5% at 27 months, with similar outcomes in younger and older patients.[5]

Although the previous data show that chemoimmunotherapy is effective in older patients—specifically the regimens of BR and chlorambucil/obinutuzumab—ibrutinib appears to have superior efficacy. The longest follow-up in the frontline setting was of 31 patients aged 65 years and older treated as part of the PCYC-1102-CA study (Safety of PCI-32765 in Chronic Lymphocytic Leukemia; NCT01105247). The overall response rate was 84%, with 23% of patients attaining a complete response. At a median follow-up of 35.2 months, median PFS was not reached, and 30-month PFS was 96%. In the only patient with progression, a Richter's transformation developed at 8 months.[6] In the RESONATE-2 trial (A Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma), which was recently published, ibrutinib was compared with single-agent chlorambucil. PFS at 18 months for ibrutinib was 90%, and 24-month OS was 98%. These data compare extremely favorably with the data that have been published for frontline studies of chemoimmunotherapy in CLL.

Equally important to efficacy in the older population, ibrutinib has been well tolerated in clinical studies. In RESONATE-2, the most common toxicities were diarrhea, fatigue, nausea, and cough. The rate of discontinuation due to toxicities was 9%. Serious toxicities included atrial fibrillation and bleeding. Atrial fibrillation often can be managed without permanent discontinuation of ibrutinib.[7] Hemorrhage usually has been associated with the use of anticoagulants, so anticoagulants should be administered with care in patients taking ibrutinib. Notably, no studies with longer follow-up have shown any evidence of cumulative toxicity, suggesting that patients may be able to stay on the drug for very long periods. In our institutional experience, infectious toxicity specifically requiring discontinuation of therapy decreased dramatically over time. Of 308 patients receiving ibrutinib mainly for relapsed disease, 16 discontinued owing to infection within the first 6 months of therapy, 7 within 6 to 12 months, and only 5 beyond 12 months, suggesting that severe infections actually are less likely to occur with a longer duration of therapy.[8]

Arguments that might be raised to support chemoimmunotherapy rather than single-agent ibrutinib as frontline therapy in older patients include cost and length of therapy. Although this drug is expensive, true economic analyses will be required to determine whether the favorable toxicity profile (potentially preventing hospitalizations, physician visits, and additional medications) and efficacy (preventing the need for additional therapies) will offset the additional direct costs. Furthermore, although therapy currently is continued indefinitely, there is the possibility that future work may identify patients who can safely discontinue ibrutinib, at least for certain periods.

> The results from RESONATE-2 easily justify the use of ibrutinib for older patients.

Additionally, it could be argued that ibrutinib has not yet been compared with a standard frontline therapy in CLL because single-agent chlorambucil can no longer be considered the standard of care. The phase 3 Alliance A041202 study (Rituximab and Bendamustine Hydrochloride, Rituximab and Ibrutinib, or Ibrutinib Alone in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia [CLL]; NCT01886872) compared ibrutinib alone vs ibrutinib in combination with rituximab vs BR in patients 65 years of age and older. Although results are not yet available, this definitive study

will establish whether ibrutinib is significantly better than BR and whether ibrutinib should be given in combination with rituximab in the frontline setting. Until these results are available, however, the results from RESONATE-2 easily justify the use of this drug for older patients.

Because of the documented efficacy and safety of single-agent ibrutinib, it should be the preferred agent at this point for the treatment of older adults outside a clinical trial. Many new therapeutic agents in cancer represent incremental changes over standards of care, but agents that target the B-cell receptor in CLL truly are a tremendous leap forward. There is still progress to be made, so clinical trials should be offered whenever possible. However, when trials are not available, single-agent ibrutinib is currently the best choice for most older patients.

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to the age of 65 years and produces a median PFS of 53.7 months.[1] Furthermore, long-term follow-up from earlier trials has shown us that this triple-drug combination is especially beneficial in patients with a mutated immunoglobulin heavy chain variable region *(IGHV)* gene, who have a 5-year PFS rate of 66.6%.[2]

Despite these findings, the majority of patients older than 60 years need a regimen that is less toxic than FCR. Fortunately, we have at least 3 very well studied treatment combinations to offer. The first is chlorambucil plus obinutuzumab (the CLL11 trial), the second is chlorambucil plus ofatumumab (Ofatumumab + Chlorambucil vs Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia [COMPLEMENT 1]), and the third is BR (Bendamustine and Rituximab in Treating Patients With Relapsed Chronic Lymphocytic Leukemia [GCLLSG CLL2M trial]). The first 2 options are based on phase 3 trials that demonstrated the long-term efficacy and safety of these combinations, with PFS times of 26.7 months in CLL11 and 22.4 months in COMPLEMENT 1).[3,4] Side effects were manageable with both of these chlorambucil-based chemoimmunotherapies, and the number of severe infections was not significantly higher than with the less-efficacious chlorambucil monotherapy. Last but not least, many patients older than 60 years are fit enough to receive a chemoimmunotherapy regimen based on bendamustine. Data from a phase 2 study have shown that the classic BR regimen results in a response rate of 84.6% in patients older than 70 years. Even patients with a decrease in renal function (creatinine clearance <70 mL/min) have a response rate of 92%.[5] The median event-free survival seen in this trial, in which approximately 50% of the patients were older than 65 years, was 33.9 months. This BR regimen was very well tolerated, with only 7.7% of patients experiencing grade 3 or 4 infections. Recently, impressive data from the GREEN trial (A Safety Study of Obinutuzumab Alone or in Combination With Chemotherapy in Patients With Chronic Lymphocytic Leukemia) have been presented, in which a combination of bendamustine and obinutuzumab was used in the frontline setting in CLL. In a subgroup analysis that included 84 unfit patients with a median age of 67.6 years, 58.9% were negative for minimal residual disease in their peripheral blood, and the median PFS was not reached.[6]

Given all of these impressive data on chemoimmunotherapy in the first-line treatment of elderly patients, we

should not prematurely discard a winning combination. All of these combinations result in high response times, long survival rates, and limited toxicities. Furthermore, no data published so far have shown a benefit from novel drugs superior to that from classic chemoimmunotherapy combinations. We should bear in mind that even RESONATE-2, which compared ibrutinib with outdated monotherapy in which chlorambucil was used as a frontline treatment of CLL, is insufficient for establishing the superiority of novel agents.[7] We need to await solid data based on a head-to-head comparison of novel agents vs chemoimmunotherapy in the frontline treatment of CLL.

In the meantime, we should not forget that chemoimmunotherapy continues for a limited period. In other words, by definition the treatment-free survival time is much longer with chemoimmunotherapy than with novel agents such as ibrutinib and idelalisib, which entail continuous administration. This is more than just an abstract secondary benefit; it may very well improve quality of life because patients are no longer reminded of their cancer diagnosis on a daily basis.

No data published so far have shown a benefit from novel drugs superior to that from classic chemoimmunotherapy combinations.

Although we know that chemoimmunotherapy causes secondary primary malignancies in a subset of patients, it is unclear what the long-term effects of novel B-cell receptor inhibitors might be. Early results regarding the development of resistance to ibrutinib and reports of highly refractory Richter's transformations are worrisome.[8,9] Patients have very poor outcomes in these cases, with a median OS as short as 3.1 months. We are also faced with the fact that drugs such as idelalisib, which have a manageable toxicity profile in the relapsed setting, can be harmful in the first-line setting. Life-threatening autoimmune conditions such as hepatitis and colitis, which had not been foreseen, developed in some patients.[10] A further "black hole" is the issue of cost. If unlimited therapy with novel drugs beginning at the initiation of treatment is formally approved for all patients with CLL, charges in the neighborhood of $130,000 per year could continue indefinitely. This raises concerns about affordability and the cost to society.[11]

Taken together, chemoimmunotherapy regimens remain the gold standard for our patients with CLL, including those older than 60 years. Chemoimmunotherapy is the first arrow we shoot, and a sharp one, but if it misses the mark, we have several others in the quiver. With further development, we may choose one of those other arrows first.

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