COUNTERPOINTS

Current Controversies in Hematology and Oncology

Should Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia Be Intensive?

Approximately 20% to 30% of adults diagnosed with acute lymphoblastic leukemia are positive for the Philadelphia chromosome, which is associated with a poor prognosis. Do these patients require intensive treatment? In this month's Counterpoints, Drs Nicholas Short and Elias Jabbour make the case for intensive treatment, whereas Dr Sabina Chiaretti makes the case for nonintensive treatment.

Intensive Treatment Is the Best Treatment for These Patients

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Outcomes for patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) used to be dismal. The response rate to chemotherapy alone ranged from 50% to 70%, and long-term overall survival (OS) was less than 20%.[1] In the era of chemotherapy-only treatment, the only way to improve the outcome of patients with Ph+ ALL was through allogeneic stem cell transplant (ASCT). Many patients are not candidates for this procedure, however, owing to lack of a donor, advanced age, or comorbidities.

The Role of Tyrosine Kinase Inhibitors

The prognosis of patients with Ph+ ALL changed with the introduction of tyrosine kinase inhibitors (TKIs) in 2000. In one study, Thomas and colleagues from our institution showed that the addition of imatinib (Gleevec, Novartis) to chemotherapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) more than doubled the 5-year survival

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Intensive Treatment Is Not Necessary, at Least in Induction

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Ph+ ALL is a clinical entity characterized by the presence of the t(9;22) (q34;q11) translocation, which creates the BCR-ABL1 transcript. This transcript, which was recognized by Nowell and colleagues back in the 1960s, is pathognomonic of both chronic myeloid leukemia and Ph+ ALL. Indeed, the recognition and causality of this transcript have led to the generation of molecules directed toward the ABL1 kinase.

In the past, Ph+ ALL was regarded as the ALL subgroup with the worst prognosis. Chemotherapy was ineffective in the majority of cases unless followed by ASCT.[1] The prognosis has changed drastically since the introduction of TKIs, now in their third generation, which lead to complete hematologic remission (CHR) in virtually all cases and have improved both OS and disease-free survival (DFS). As a result, OS and DFS in Ph+ ALL are now similar to those of other ALL subtypes—and better in the elderly—and soon may even become superior across all ages.

In light of what we now know, we are seeking the answers to 3 major questions: (1) Do we really need intensified treatment, at least in induction? (2) Is intensified treatment the only way to further increase minimal residual disease clearance? and (3) Do all patients require ASCT?

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Intensive Treatment Is the Best Treatment for These Patients *(cont)*

rate from less than 20% to 43%.[2,3] Since then, several studies have been published in which imatinib plus intensive chemotherapy produced long-term survival rates in the range of 30% to 50%.[4,5] For example, in a large prospective series by the Medical Research Council of the United Kingdom Adult ALL Working Party, the addition of imatinib to chemotherapy clearly improved outcomes.[5]

A French study compared a reduced-intensity chemotherapy approach vs hyper-CVAD as induction and consolidation treatment for adults with Ph+ ALL.[6] This study found that these approaches had equivalent efficacy, but fewer induction deaths occurred in the less intensive arm. This supported the use of nonintensive chemotherapy in combination with a TKI. The caveat, however, is that imatinib was given 2 weeks on and 2 weeks off in this study, which is not the best way to combine chemotherapy with a TKI. Continuous rather than intermittent TKI administration has been shown to be a more efficacious way to deliver the TKI in Ph+ ALL.[7]

We at MD Anderson have moved from imatinib to the more potent second-generation TKI dasatinib (Sprycel, Bristol-Myers Squibb) in combination with hyper-CVAD.[8] This combination led to a complete molecular response (CMR) in 65% of patients and a 5-year OS rate of 46%. A French study by Rousselot and colleagues took a different approach in patients who were not fit to receive chemotherapy.[9] A total of 71 patients received dasatinib plus a corticosteroid, followed by consolidation treatment. The complete remission (CR) rate was 94%, the 5-year event-free survival (EFS) rate was 27%, and the 5-year OS rate was 35%. Emergence of the *T315I* mutation was common among patients at the time of relapse, affecting 63% of these patients.

In Italy, Chiaretti and colleagues studied dasatinib as part of a nonintensive regimen in fit patients with a median age of 42 years.[10] Patients received dasatinib and a corticosteroid for 3 months, and those who achieved a CMR continued to receive dasatinib alone. Patients who did not achieve a CMR received more intensive chemotherapy and/or ASCT. The study showed that with the nonintensive approach, the CMR rate was 19%, with a 3-year OS rate for the entire cohort of 58%. Patients who achieved CMR had better outcomes than those with lesser outcomes (disease-free survival rates of 75% vs 44%, respectively). Furthermore, a multivariate analysis concluded that CMR independently predicted outcome.

These results suggest that we should strive for treatment strategies in Ph+ ALL that improve the CMR rate and prevent the *BCR-ABL1 T315I* mutation from emerging. The key to improving the CMR rate is with more intensive chemotherapy regimens that incorporate more potent TKIs. The key to preventing acquisition of this mutation is to use the potent later-generation BCR-ABL1 inhibitor ponatinib (Iclusig, Ariad).

Ponatinib is superior to dasatinib, nilotinib (Tasigna, Novartis), and imatinib in inhibiting the BCR-ABL1 gene product, so we combined ponatinib with hyper-CVAD for our next study.[11] At the beginning of the study, we used 45 mg per day of ponatinib. However, after 2 vascular events occurred among the first 30 patients, we amended the study and reduced the ponatinib dose to 45 mg per day for the first 2 weeks, followed by 30 mg per day until achievement of CMR, and then followed by 15 mg per day indefinitely. We have treated nearly 60 patients (median age, 54 years) with this regimen, and have produced a CMR rate of 79% and a 3-year survival rate of 80%, results that are superior to any other previous reports in Ph+ ALL. Furthermore, when we performed an analysis at 4 months after ASCT, we did not observe a difference in favor of transplant. This suggests that ASCT may not be necessary in patients treated with intensive chemotherapy plus ponatinib. Notably, we also saw no further vascular events after we modified our regimen to reduce the dose of ponatinib.

Using data from our institution on hyper-CVAD plus dasatinib or ponatinib, we have performed a propensity score analysis of these two phase 2 trials in order to compare the relative efficacy of each of these regimens.[12] In a matched population, the ponatinib-containing regimen was associated with a significant improvement in the 3-year survival rates compared with the dasatinib-containing regimen (83% vs 61%, respectively). This improvement was likely driven by the deeper molecular responses achieved with ponatinib.

The Value of Intensive Chemotherapy

We at MD Anderson take the approach of intensive chemotherapy plus ponatinib, whereas Chiaretti and others use nonintensive chemotherapy plus a TKI. The CR rate with both approaches is similar, at nearly 100%, but the CMR rate is approximately 80% with our regimen, compared with only 20% with the nonintensive regimen. Notably, CMR is an important therapeutic outcome, and our group recently reported on its prognostic impact in Ph+ ALL.[13] In this analysis of patients with Ph+ ALL who did not undergo ASCT in first remission, achievement of

CMR by 3 months was the only factor associated with OS. The 4-year OS rate for patients who achieved CMR was 66%, and the impact of CMR was independent of the TKI received.

Based on these findings, we believe that ASCT is not required in first remission for patients who achieve a CMR and who continue on indefinite TKI therapy. Using this risk-adapted approach, we are able to perform far fewer of these procedures, and thus spare many patients the associated morbidity and mortality of ASCT. The strong association of deeper molecular responses with outcomes in Ph+ ALL highlights the importance of choosing a regimen with the best chance to induce an early CMR. The use of intensive chemotherapy in combination with a later-generation TKI results in higher rates of CMR than do less intensive regimens, and therefore we use this approach for all patients with Ph+ ALL who are fit to receive intensive treatment.

New Approaches

Of course, we hope to someday eliminate the need for intensive chemotherapy without jeopardizing efficacy. One agent that may prove to be effective in this regard is blinatumomab (Blincyto, Amgen). Blinatumomab is a bispecific T-cell engager that targets CD19 on leukemic blasts. It has been approved for use in relapsed or refractory Ph-negative ALL. The drug has also been tested in the setting of relapsed or refractory Ph+ ALL. In a study of 45 patients, the response rate was 36%, with 88% of responders achieving minimal residual disease negativity.[14] The next step in research should be to examine this agent in combination with ponatinib as first-line treatment for Ph+ ALL.

In conclusion, we think that a combination of intensive chemotherapy and a TKI is necessary for fit patients with Ph+ ALL. The TKI should be administered early, concomitantly with chemotherapy, and indefinitely, rather than starting late or eventually stopping TKI treatment. Based on the data available today, ponatinib is a very efficacious agent for Ph+ ALL, able to achieve a CR rate of 100% and a CMR rate of 79% when combined with intensive chemotherapy. We feel that ASCT should be reserved for patients in first remission who have not achieved a CMR at 3 months or later. The use of intensive chemotherapy plus a TKI allows the achievement of the highest possible CMR rate, and therefore minimizes the need for ASCT. In the future, we eventually hope to get rid of the need for intensive chemotherapy by using a combination of a TKI plus a novel agent such as blinatumomab or another new monoclonal antibody (eg, inotuzumab ozogamicin).

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Regimens Based on Nonintensive Induction Treatments

The incidence of Ph+ ALL increases with age, with more than 50% of cases being detected after the fifth decade of life.[2,3] This has important clinical implications because elderly patients usually have several comorbidities, and therefore are not considered fit to receive intensive treatment. For this reason, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA group) carried out a trial (GIMEMA LAL 0201-B) in elderly patients using an induction strategy based on imatinib. Patients received corticosteroids for prophylaxis of central nervous system (CNS) complications, but did not receive systemic chemotherapy. All 29 patients (median age, 69 years; range, 61-83 years) enrolled in the study achieved a CHR, and a molecular remission was documented in 1 additional patient. Although this study did not address treatment after remission because of the age of the patients, it represented the first proof of principle of the efficacy of an induction treatment that did not include systemic chemotherapy.[4]

The GIMEMA LAL 0904 trial was a natural extension of the 0201-B trial that enrolled younger patients (n=49; median age, 45.9 years; range, 16.9-59.7 years). The same induction strategy was applied, followed by a consolidation cycle with high-dose cytarabine plus mitoxantrone (HAM) and, whenever possible, by allogeneic or autologous SCT. Similar results were obtained, with a CHR rate of 96% after induction with imatinib alone, and of 100% after HAM. The 5-year OS was 48.8% and the 5-year DFS was 45.8%; these represent the best long-term survival rates so far reported[5] except for those reported at 2 years with the third-generation TKI ponatinib.[6]

GIMEMA LAL 1205 took a similar approach, although it used the second-generation TKI dasatinib, a more potent TKI that has the limitation of being ineffective toward the gatekeeper *T315I* mutation.[7] All of the patients in this trial (n=55; median age, 53.6 years, no upper age limit) achieved a CHR upon induction. In addition, the BCR-ABL1 level dropped below 10^{-3} in 22.7% of cases.

Finally, GIMEMA LAL 1509 also used dasatinib followed by chemotherapy (manuscript in preparation). In this trial, 58 of 60 (97%) patients achieved a CHR at the end of induction, DFS was 58.3% and OS was 49% at 30 months, and a CMR (ie, BCR/ABL1/ABL1=0) was obtained in 19% of cases.

Other groups have provided similar results. The Programa Español de Tratamiento en Hematología (PETHEMA) Ph-08 trial,[8] which was based on a less-intensive chemotherapy regimen and an increased dosage of imatinib, led to CHR rates of 100% among the 29 patients enrolled (mean age, 42 years), a CMR in 39% of cases, and improved 2-year EFS compared with historical controls (67% vs 37%, respectively).

The European Working Group on Adult ALL (EWALL) study recently used less-intensive chemotherapy plus imatinib in elderly patients (n=71; median age 69 years).[9] The CHR rate in this study was 96%, a total of 20% of patients achieved a CMR upon induction, and the 5-year OS rate was 36%.

Finally, a formal comparison was recently described by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL).[10] The authors compared the results obtained in 268 patients treated either with reduced-intensity chemotherapy plus imatinib or with the standard imatinib/hyper-CVAD regimen, and showed that CHR rates were significantly better in patients receiving deintensified treatment (98% vs 91%). Molecular responses were comparable in both arms, and a trend toward slight superiority that was not statistically significant was observed in 5-year OS (48.3% vs 43.0%) and EFS (42.2% vs 32.1%).

Taken together, these results lead to 3 important conclusions: (1) virtually all patients can achieve a CHR upon induction; (2) in some cases, depending on the potency of the TKI used, a major molecular remission and/or CMR can be achieved, pointing to the role of nonintensive approaches in inducing and sustaining molecular responses; and (3) in all the trials described above, no or very few deaths in induction were recorded compared with historical controls. (There were no deaths in the GIMEMA trials or the PETHEMA Ph-08 trial, and just 1 death occurred in the GRAALL study.) This demonstrates that a nonintensive strategy has the advantage of avoiding toxicity, which all studies have reported with more intensive treatment.

Ongoing and Future Trials

Ponatinib, the experimental third-generation pan-TKI that is active against the gatekeeper *T315I* mutation, currently is providing impressive results. Researchers at the MD Anderson Cancer Center recently published the results of a trial based on the combination of ponatinib and the hyper-CVAD regimen.[6] Of the 37 patients enrolled (one of them was already in CR at the time of enrollment), all achieved a CR—with 26% achieving a CMR upon induction. The 2-year EFS and OS of 81% and 80.4%, respectively, are extremely encouraging. Nevertheless, 6 deaths related to toxicity were recorded among patients who had a CR.

In keeping with the GIMEMA strategy, we are currently completing a trial for elderly patients or those who

are unfit to undergo intensive treatment (GIMEMA LAL 1811). This treatment is based on induction with ponatinib (45 mg) and corticosteroids for CNS prophylaxis, followed by ponatinib until progression or until a serious adverse event is recorded. Although preliminary data appear extremely promising, the study is still enrolling patients at press time.

One patient is being treated here at Sapienza University, an 85-year-old woman who was diagnosed with Ph+ ALL in February 2016 and achieved a CMR at day 22 of treatment. We temporarily interrupted ponatinib treatment because of an episode of hypertension, and restarted the agent 2 weeks later at a reduced dose of 30 mg. At 6 months from diagnosis, her clinical status is excellent and she has a persistent CMR. This finding reinforces the notion that nonintensified treatment is at least as effective as intensified therapy, without producing dose-limiting toxicities.

Conclusion

In conclusion, although the role of consolidation treatment with ASCT still represents the best curative option, at least for the time being, the data hereby reported clearly show that a chemotherapy-free induction or a nonintensified regimen provide the best overall results. Finally, the introduction of novel immunotherapeutic agents, such as blinatumomab, is likely to improve further the outcome of these patients, and might allow avoidance of ASCT in a proportion of cases.

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