

## A chemotherapy-free regimen for Philadelphia chromosome-positive acute lymphoblastic leukemia: are we there yet?

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Novel therapies are revolutionizing the treatment strategies for Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). Ten years ago, the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) ALL Working Party pioneered a chemotherapy-free induction regimen using the dasatinib-steroid combination,<sup>1</sup> which brought about complete hematological remission (CHR) in all 53 evaluable patients<sup>2</sup> and complete molecular response (CMR) in ten of them (18.8%).

In this issue, final results of a subsequent LAL1509-GIMEMA prospective single-arm trial are reported.<sup>3</sup> The treatment protocol included 1-month induction with the aforementioned combination, followed by dasatinib extension until day 85. The post-remission regimen was assigned based on the minimal residual disease (MRD) status. Of the 60 enrolled patients (median age 41.9 years [range, 18-60]), those who achieved CMR were subject to dasatinib maintenance with no further intensification. The majority of patients (47 of 60; 78%) achieved CHR, while testing MRD-positive post-induction. These patients were assigned to allogeneic stem cell transplantation (allo-SCT) with or without consolidation chemotherapy. Patients ineligible for transplantation were consolidated with chemotherapy only. No induction deaths were reported and the CHR rate by day 85 was 97%, with CMR achieved in 11 of 60 (18.3%) patients. At a median follow-up of almost 5 years, overall survival (OS) and disease-free survival (DFS) were 56.3% and 47.2%, respectively.

Are these impressive data sufficient to set the stage for a new standard of care in Ph+ALL? One of the critical achievements of these two studies, that should be taken into consideration, is the absence of induction deaths among the 113

patients treated. To that end, future Ph+ALL treatment protocols should be designed with the aim to maintain such a minimal induction-related mortality rate. However, this attractive low-intensity induction regimen may be unsuitable for higher-risk Ph+ALL patients. In the LAL1509-GIMEMA protocol, the post-induction MRD status has been the sole factor used to stratify patients for intensive consolidation followed by allo-SCT *versus* dasatinib maintenance only. Yet, the clinical significance of MRD results depends on a variety of patient- and treatment-related parameters.

Based on data from previous ALL studies, the Food and Drug Administration has accepted an MRD level of less than 0.01% as a surrogate efficacy endpoint for new drugs in ALL.<sup>4</sup> Surprisingly and disappointingly, in the current trial, four of 11 (36%) patients who achieved CMR with the dasatinib-steroid induction eventually relapsed. Three of these relapses were diagnosed early at a molecular level and therefore never fulfilled the former criteria of relapse. This must raise a red flag and a message regarding the complexity of MRD clinical interpretation should be played out loud. MRD negativity is not synonymous to cure but it is rather its biomarker. No matter how sensitive the available tests are, there is still room for residual disease presence at a level below the threshold of detection. Thus, ultimate degrees of disease eradication for patients who achieve MRD negativity following intensive and less intensive induction may be different. A negative MRD result following intensive induction reflects an even deeper response than the sensitivity cutoff of the test used. This should not be extrapolated to the outcome prediction following less intensive protocols when the actual level of response below the MRD negativity cutoff may be lower (Figure 1). Not only the specific induction protocol but also

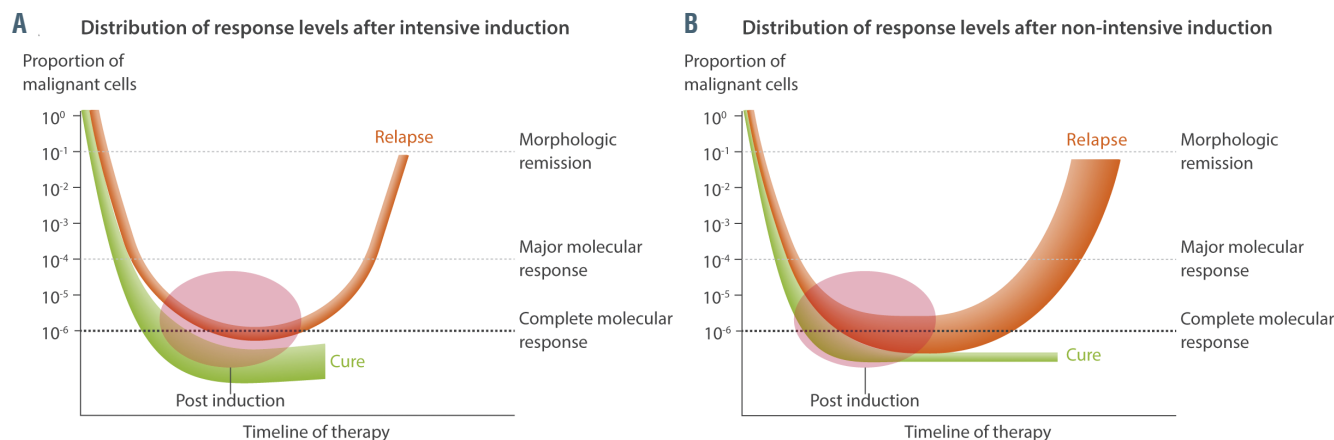


Figure 1. Response after intensive and non-intensive induction in a population of Philadelphia chromosome-positive acute lymphoblastic leukemia patients. (A) Distribution of response levels after intensive induction. (B) Distribution of response levels after non-intensive induction. The distribution of the actual depth of response across patients who achieved minimal residual disease negativity following intensive and non-intensive induction differs and so does the risk of relapse.

the characteristics of the patient population should be taken into account. For instance, in Ph-negative ALL, achievement of identical laboratory major molecular response levels following treatment with intensive chemotherapy and tyrosine kinase inhibitors, was shown to predict considerably different relapse-free survival rates for newly diagnosed *versus* relapsed patients (26.1 vs. 12 months, respectively).<sup>5,6</sup> Notably, progression-free survival for relapsing patients who achieved MRD negativity with inotuzumab ozogamicin treatment was as short as 8.6 months.<sup>7</sup> Thus, in different clinical settings, identical laboratory results may be associated with completely different predicted outcomes.

The LAL1509 trial, while demonstrating feasibility of a chemotherapy-free regimen for some patients, has also highlighted that biological differences within the Ph+ALL patient population go far beyond the presence or absence of *BCR/ABL* mutations such as T315I. In this trial, patients presenting with genetic aberrations in *IKZF1* plus *CDKN2A/B* and/or *PAX5* (*IKZF1*<sup>+</sup>) demonstrated a relapse-free survival rate of 0%. This combination of genetic abnormalities is known to portend poor prognosis even in patients undergoing allo-SCT. Yet, the relapse-free survival rates reported in previous studies using intensive induction regimens have been better.<sup>8</sup> Moreover, the GIMEMA group has lately reported results of using a still more attractive combination of steroids, dasatinib and blinatumomab,<sup>9</sup> that has led to considerable improvement in the survival of all patients, including those presenting with *IKZF1*<sup>+</sup> aberrations.

What have we learned from the current trial? First, induction death in Ph+ALL is preventable and for some patients even non-intensive induction should be considered. Second, the way MRD negativity is achieved influences its clinical implications. Third, routine screening for *IKZF1*<sup>+</sup> abnormalities is advised and may be considered when the intensity of an induction regimen is selected. And last but definitely not least, a combination of steroids, tyrosine kinase inhibitors and blinatumomab, given as first-line therapy, is an attractive option for

Ph+ALL patients and is currently being studied as part of a large intergroup prospective phase III trial, led by ECOG-ACRIN, EA9181 (clinicaltrials.gov. Identifier: NCT04530565).<sup>10</sup>

### Disclosures

No conflicts of interest to disclose.

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