- The investigators were able to detect an informative clonotypic sequence in 83% of patients in this study. Not surprisingly, the yield was higher for those with fresh frozen vs formalin-fixed paraffin-embedded tissue and also for those with more tissue available, but even in their real-world validation cohort, a clone was detected in 71% of patients. As long as sufficient paraffin-embedded tissue was available from an excisional biopsy, the chances of identifying a clonotype were high. Importantly, the rate of detection did not appear to be related to stage at presentation, so this technique has potential even in those patients with limited stage disease.
- Detection of molecular disease in the plasma was consistently more sensitive than in circulating tumor cells and was also a more reliable marker of disease, at least in the relapse setting, than serum lactate dehydrogenase (LDH). At present, serum LDH is probably the most widely used serum tumor marker in aggressive B-cell non-Hodgkin lymphoma, but its utility in this context has never been validated prospectively. In this study, the authors demonstrate that plasma levels of tumor DNA correlated more closely with tumor volume than did serum LDH.
- In general, sequential levels of circulating tumor DNA closely followed changes in tumor volume, assessed by functional imaging. Escalating levels predicted radiologic and clinical relapse or occurred concurrently with clinical relapse in most patients. The figure demonstrates 2 illustrative patients in which increased levels of circulating tumor DNA correlated with relapse/progression on CT/PET, with varying lead times.
- In the posttreatment surveillance setting, the specificity of molecular disease detection in the plasma was 100%. This suggests that measurement of circulating tumor DNA overcomes the major limitation of functional imaging in the surveillance context: the unacceptably high false-positive rate.

Although these preliminary data are promising, there are some limitations in the present study. The sample size is quite small and is heterogeneous with respect to disease subtype and treatment. The analyses of the relationship between functional imaging and tumor DNA were not adjusted for treatment: this will be important to investigate in future studies because existing data suggest that the predictive value of functional imaging may be treatment dependent.[7] Although the authors conducted a real-world validation of their ability to detect clonotypic sequences, it's not clear how the success rate of this technique will vary between laboratories, and how reproducible the results will be across different centers. In view of the small sample size, the authors were not able to investigate the potential influence of disease-related factors such as molecular subtype: this will be an important question to address in future studies.

Whether Ig-HTS will prove to be a real advance in the setting of response assessment and response-adapted therapy is unclear. Early assessment of response will prove beneficial only if there is an effective second-line therapy for nonresponders. It will be important to demonstrate that earlier detection of relapse translates to an improved outcome for patients. As described in a previous report, this technique might also be applicable to the detection of minimal residual disease (MRD).[8] The use of MRD to guide therapy has, until now, not been evaluated in DLBCL because of the lack of a reliable assay using peripheral blood.

Where this technique is likely to have the most immediate impact is in the posttreatment surveillance setting. Results from this study suggest that Ig-HTS in plasma is a noninvasive investigation with high specificity, closely correlated with tumor burden, and demonstrates a temporal relationship to radiologic and clinical relapse. The lead time associated with molecular detection may not have a major impact on subsequent survival, but the preliminary data in this study suggest that HTS may replace routine imaging or at least restrict its use to those patients in whom the suspicion for recurrence is highest. This will limit radiation exposure and reduce the unnecessary anxiety and interventions that accompanying false-positive scans. If the results of this preliminary study are confirmed, it will change practice.

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Chalandon et al, page 3711

# Time to tune the treatment of Ph+ ALL

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In this issue of *Blood*, Chalandon et al report the results of a prospective randomized study comparing standard vs less-intensive chemotherapy, both combined with imatinib, for patients with newly diagnosed Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL). They show that the less-intensive therapy reduces early mortality without impairing efficacy, resulting in a significantly higher hematologic complete remission (CR) rate and an equivalent major molecular response (MMolR) rate.[1]

The advent of tyrosine kinase inhibitors (TKIs) has completely changed the therapeutic landscape of Ph+ ALL.[2] A TKI combined with chemotherapy is now used as the treatment of choice for newly diagnosed Ph+ ALL patients; however, many unresolved issues are still present. Indeed, it is more correct to say that only a few clinical questions are addressed by currently available evidence, and even fair to say that all we know is that this therapy should be used. This equivocal situation is primarily attributable to the lack of prospective randomized controlled studies, and the rarity of the disease makes it difficult to conduct a large-scale trial. To my knowledge, there are only a couple of published prospective studies that enrolled a 100 or more patients,[3,4] all of which were nonrandomized phase 2 trials.

By overcoming such practical difficulties, Chalandon et al from the Group for Research on Adult Acute Lymphoblastic Leukemia successfully completed the largest trial ever, containing 270 newly diagnosed Ph+ ALL patients aged 18 to 59 years, and attempted to address the important question of whether intensive chemotherapy is really necessary for induction therapy incorporating imatinib.[1] After enrollment, patients were randomized to receive imatinib combined with either less-intensive chemotherapy consisting of vincristine and steroids (investigational arm) or a more intesnse regimen of fractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone (control arm). For the second course, patients in both arms received a similar chemotherapy consisting of methotrexate, cytarabine, and imatinib, followed by allogeneic hematopoietic cell transplantation (HCT), if eligible. In the absence of a suitable donor, those who achieved MMolR after the second course proceeded to autologous HCT. The primary end point of the study was the MMolR rate after the second course, which was 66.1% for the investigational arm and 64.5% for the control arm ($P = .88$), meeting the predefined criteria for noninferiority of the investigational arm. The hematologic CR rate was significantly higher in the investigational arm than that in the control arm (98.5% vs 91.0%, $P = .006$) because of reduced early mortality for the former. Other secondary end points, including event-free survival (EFS), relapse-free survival, cumulative incidence of relapse, cumulative incidence of nonrelapse mortality, and overall survival (OS), did not differ between arms.

Since the initial reports of imatinib used in conjunction with chemotherapy for Ph+ ALL, imatinib has been preferentially incorporated into standard ALL-type chemotherapy. Although this combination is able to raise CR rates to around 95%, early deaths occur in up to 5% of patients, which represents the primary reason for failure to achieve CR.[3-7] The strategy to combine imatinib with standard chemotherapy has been challenged by subsequent studies that investigated the use of a TKI alone or in combination with steroids.[8-10] Ottmann et al evaluated imatinib monotherapy in 27 patients older than 55 years of age, and observed CR in 26 patients and partial remission in the remaining patient.[8] Vignetti et al conducted a study of imatinib and steroids in 29 patients older than 60 years of age, in which all of them achieved CR.[9] Foà et al reported that all of their 53 patients over the age of 18 years treated with dasatinib and steroids achieved CR.[10] These findings raise a concern that intensive chemotherapy during induction may not be beneficial and even harmful, although this notion has been inconclusive till now. The present study reported by Chalandon et al provides robust insights into this issue.[1] Compared with the control arm, the less-intensive arm yielded a significantly higher hematologic CR rate and a similar MMolR rate after the second course. Somewhat unexpectedly, both arms showed similar MMolR rates even after the first course (43.1% vs 45.5%, $P = .78$). This study also reports several significant findings with respect to postremission therapy that upfront allogeneic HCT leads to an improvement in long-term outcomes and that autologous HCT is effective in patients achieving MMolR at an early stage of treatment. However, despite these achievements, the overall prognosis for their patients is not satisfactory enough because the 5-year EFS and OS rates remained at 37.1% and 45.6%, respectively. This confronts us with the fact that there is much room for improvement, particularly in postremission therapy.

In conclusion, this study represents a big step forward in the treatment of newly diagnosed Ph+ ALL, and induction therapy has moved toward a more refined way. Future clinical research needs to focus on preventing a relapse for these patients.

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