Inclusion and response criteria for clinical trials in relapsed/refractory acute lymphoblastic leukemia and usefulness of historical control trials

We thank Paul Gaynon for his commentary on our international reference analysis of relapsed/refractory (R/R) adult acute lymphoblastic leukemia (ALL). The commentary highlights a certain lack of standardization with regard to inclusion criteria and endpoints of clinical trials for R/R ALL in adults and children, and also elucidates the potential risks of bias in historical comparator studies.

As reflected in the methods section of our manuscript, there is broad agreement in first-line trials for adult ALL that a relapse is defined as 'detection of more than 5% blast cells in the bone marrow after prior achievement of complete remission (CR) or unequivocal demonstration of extramedullary leukemia involvement'. The European Working Group for Adult ALL (EWALL) has documented this statement in a consensus recommendation,[1] with the additional explanation that 'in case of 5-20% blasts cells during the intensive treatment phase and/or during regeneration, the bone marrow assessment should be repeated one week later in order to distinguish bone marrow relapse from regeneration phenomenon'. The cited definition is based on international recommendations for outcome parameters in acute myeloid leukemia.[2,3] In particular, the criteria documented by Cheson and colleagues[3] are used as the standard of care (SOC) for adult acute leukemias in many countries. The threshold of 5% offers the opportunity to start salvage therapy in cases of unequivocal relapse diagnosis earlier and with lower leukemia burden, which may be an advantage for patients. The higher threshold of >=25% blasts as used in pediatric ALL may in part be associated with the higher incidence of hematogones in regenerating marrow which might be confused with leukemic blast cells.[4]

Based on these 'standards' for adult acute leukemias, inclusion criteria for pivotal trials in adult ALL were mostly defined at the threshold of 5-10% blast cells,[5-8] whereas trials in pediatric patients were defined at a threshold of 25%.[9-11] More recently, some trials did not even define the presence of relapse at all. Thus, studies with chimeric antigen receptor (CAR) T cells included patients with 'measurable disease' and also comprised patients with either hematologic relapse (without further specification) or positive minimal residual disease (MRD).[12,13] The lack of standardization in terminology can unfortunately be detected for outcome parameters as well, with variations for the definitions of CR/CRi/CRh/CRp etc.

The role of leukemia burden in trials with new compounds is, nevertheless, of interest. The published trials with blinatumomab and inotuzumab in adult ALL demonstrated that around one third of the patients had bone marrow (BM) blast counts below 50% at study entry.[5,6] The CR rates for inotuzuamb were reported as 87% *versus* 78% for BM blasts below or above 50%, respectively; for SOC the corresponding rates were 41% *versus* 24%. In this trial patients with peripheral blasts above 10.000/µl were excluded.[5] In the phase II blinatumomab trial the response rates were 73% *versus* 29% in patients with BM blasts below and above 50%, respectively.[6] We agree that leukemia load may play a role in response rates, particularly for single drug immunotherapies. However, the relevant threshold may be higher than 25%. The blast count in bone marrow is, however, only one measure in this respect. To create a more informative model, lactate dehydrogenase (LDH), peripheral blast count and potential extramedullary involvement should be considered in addition. We are far from the standardization of such models, which may be important not only for the prediction of response rate but also for toxicities.

We think that a combined definition of CR and failure/relapse with cytologic and molecular/flow cytometry criteria would be helpful in the future. This would, however, also require the integration of reference laboratories. We are on the way to such internationally agreed definitions for MRD-based response evaluation.[14] Based on these definitions and standardized MRD assays, new compounds can be tested in clinical trials on patients presenting with MRD - prior to the detection of hematologic relapse - as was successfully performed in two trials with blinatumomab in MRD-positive disease.[15,16]

The second remark refers to the patient population in the historical comparator study. Clearly, inclusion criteria of clinical trials lead to selection, to some extent, and some patients from the historical comparator group may not have been included in a phase II trial. However, many inclusion/exclusion criteria of clinical trials are focused on safety aspects e.g., prior central nervous system (CNS) disease or current graft-*versus*-host disease GvHD, as in the blinatumomab trials.[6] These criteria are unlikely to be linked to lower response rates. In other words, for a comparison of real-world data with clinical trial data, principally the disease-specific inclusion criteria should match; we tried to come as close as possible to this approach in our comparative analysis.[17] Nevertheless, we have addressed this limitation of our analysis very clearly in the discussion.

The improvement of outcome over time is very limited in relapsed adult ALL. Overall, in the time period reported, nearly no promising new compounds became available for adult ALL. The reported CR rates for clofarabine or liposomal vincristine were only around 20%.[10,18] The likelihood that patients from our databases were included in such trials was rather low and we don't have this information available in the dataset. One major reason for the lack of improvement is the fact that approximately 80% of relapses in adult ALL are early relapses during intensive therapy,[10] which usually do not benefit from chemotherapy salvage.

It is important to mention that one of the primary goals of our joint analysis was to elucidate outcomes in subtypes of relapsed ALL, chiefly by comparing early and late relapses, different age groups, refractory relapses, and more general issues such as the role of stem cell transplantation. The response rates in our historical study varied between 11% to 41%, depending on the line of salvage and type of relapse.[20] This observation is very important for the appropriate interpretation of trials with new compounds, because outcomes may vary depending on the type of relapses included in the trials, e.g., poorer results in trials with a high proportion of early, refractory relapses or relapses after transplant. We consider the bias of selected relapse categories in pivotal clinical trials far more important than the bias induced by slightly different thresholds for bone marrow involvement or general inclusion or exclusion criteria.

The results of our historical comparator study were very recently confirmed by results from two phase III randomized clinical trials with new compounds *versus* a randomly allocated SOC in relapsed/refractory ALL. More than 300 adult relapse patients were treated according to unsatisfactory SOC regimens without the option for crossover. SOC treatment yielded 19% CR and

28% CR/CRh/CRi in the blinatumomab trials with selected unfavorable relapses.[21] The randomized inotuzumab trial SOC showed 17% CR and 29% CR/CRi for a patient population with different relapse characteristics.[5] Both studies also had different definitions for SOC; nevertheless SOC outcomes were similarly poor. Even patients' decisions underline the questionable design of such trials, with a 12%[5] and 19%[21] withdrawal of consent in the SOC arms. Overall, results with SOC within clinical trials were well in the range of the historical data compiled in our study, which argues against major effects of patient selection in clinical trials for R/R adult ALL.

Academic study groups should enhance efforts to provide well documented standard of care registries and it should be in the interest of regulatory bodies and health care providers to support these initiatives. This will become even more relevant for rarer subgroups of ALL such as T-cell acute lymphoblastic leukemia (T-ALL) or certain molecularly defined subtypes, in which randomized trials will become impossible. All academic expert groups should collaborate with the definition of new clinical trial designs allowing parallel collection of appropriate safety data, efficacy data and provide, as much as possible, advantages to patients in life-threatening situations who are in need of new effective treatment approaches.

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