EDITORIAL

Minimal Residual Disease in Pediatric Precursor-B Acute Lymphoblastic Leukemia

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Survival of pediatric acute lymphoblastic leukemia (ALL) continues to improve over last three decades. Current survival rates in advanced centers are nearly 90% [1]. In India, the overall survival in pediatric ALL varies from 46-80% [2]. Most improvements in ALL are not due to advent of new medicines but secondary to treatment refinements, which also include reduction of therapy for low-risk patients thereby reducing toxic mortality [3].

Most children with ALL attain a morphologic remission after induction chemotherapy. Many children will eventually relapse due to residual leukemic cells that are below the limits of detection using conventional morphologic assessment. This residual leukemia is termed as minimal residual disease (MRD), and can be evaluated using multicolor flowcytometry or polymerase chain reactions [4].

Age at diagnosis, initial white blood cell count and cytogenetics are often used to stratify children into standard and high-risk ALL to ascertain the appropriate treatment protocol. It is imperative to revisit the chemotherapy protocol based on the response to initial therapy. MRD detection is an important diagnostic modality in this regard [5]; children with high MRD in either risk groups do not do well.

A large data of 7,430 children with ALL demonstrated that 5-year disease-free survival was significantly higher among MRD-negative compared to MRD-positive children (89% *vs* 72%). The MRD-positive children are candidates for further intensification of therapy and consideration of allogenic bone marrow transplantation. MRD also trumped morphologic evaluation of bone marrow on day-14. Disease-free survival was similar if children became MRD-negative on day-29. These results suggest that MRD status using a threshold of 0.01 percent at the end of induction obviates the need for bone marrow analysis at day-14 [6].

At the same time there are a lot of children with standard risk ALL who are MRD-negative at defined time points. These are the children for possible reduction in intensity of therapy. A large trial of over 3000 children and young adults randomized MRD-negative patients to receive two or one delayed intensification therapies. Both arms had similar event-free survival (94.4% *vs* 95.5%), overall survival and rate of relapse at five years [7]. Thus, MRD may be used to de-escalate therapy in certain children. Children's Oncology Group (COG) data suggest that 50% of relapses still occur in children with standard risk B-ALL who were MRD-negative [8]. We therefore need to be cautious in de-escalating therapies in MRD-negative children till further data emerges.

Bommannan, *et al*. [9] report their data on mid-induction peripheral blood MRD in a small cohort of 40 children with a follow-up reasonable enough to pick at least early relapses. It is heartening to see few things stand out from their data. We always talk about resource constraints in our country. Here, we have six-color flowcytometry available for MRD evaluation. Disease load is certainly more in bone marrow compared to peripheral blood suggesting that bone marrow continues to remain gold standard for disease evaluation. They report high rates (62.5%) of MRD-positivity in bone marrow on day-15. This is a high proportion and signifies delayed blast clearance from bone marrow, or using lower threshold of 0.01% as positivity. Children who were MRD-negative did not experience any relapses and few relapses in MRD-positive patients probably due to early analysis. It is possible that many of D15+ patients would have become MRD-negative by D30 of induction chemotherapy. It is quite possible that more D15 data emerges with different cut-off for us to decide in terms of escalation or de-escalation of therapy.

The interpretation of MRD is complicated and must take into account the timing of assessment, level of MRD and sensitivity of test being used. The main reason to perform MRD assessment is to assess response and be able to act on the information like day-30 of induction

when treatment phase changes. Therefore, timing of MRD assessment is crucial. MRD cut-off of day-30 is not relevant for day-15 analysis.

Most ALL protocols are made with inputs from lot of research. Each protocol will have defined a different time point for MRD analysis and a different cut-off. We should not mix and match protocols for these analyses. Rectifications are inbuilt into current protocols based on MRD analysis. Another interesting aspect was the message that one should stick to protocol. As in this study, children with high-risk ALL (after addition of daunorubicin) did as well as their standard risk counterparts in terms of response to therapy and lowering of MRD [9]. This study provides relevant data amongst Indian children with ALL, and suggests a good correlation between peripheral blood and bone marrow MRD. A long term follow-up of this cohort will generate data, which will make us wiser.

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