Clinical Relapse versus Treatment failure The case for surveillance for reappearance of minimal measurable disease in pediatric patients with higher risk B-ALL.

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Despite impressive progress in childhood acute lymphoblastic leukemia, an urgent clinical need remains. Patients still relapse and outcomes after relapse have changed little between 1996- 2006 and 2004 – 2014.[1] Despite progress with late marrow relapse (1^{st} remission (CR1) > 36 months), treatment of early relapse (CR1 < 36 months) remains unsatisfactory,[2] especially in patients deemed higher risk at diagnosis, such as adolescents and young adults (AYA's).[3]

Progress to date derives from improved primary therapy. Further improvements in primary therapy have an ever-increasing price. Going from 50% to 70%, a 40% reduction in relapses, 5 patients need to be treated to prevent one relapse. Similarly, going from 75% to 85%, again a 40% reduction relapses, 10 patients need to be treated to prevent one relapse. With improving outcomes with primary therapy, we are facing an increasing number needed to treat for further improvement.[4] All patients need to bear the burden of a novel intervention to benefit an ever smaller percentage. Not all interventions are successful.

Recent experience suggests that we are reaching the limits of "intensification" of therapy, despite improvements in supportive care.[5] For some patients such AYA's, we may have surpassed tolerable limits. Querying the Pediatric Health Information system database, Gupta et al found a higher incidence of intensive care unit stays and increased toxicities in almost every organ system for AYA's.[6] Serious complications may prevent delivery of best care, resulting in relapse.

Personalized molecularly targeted medicine is complicated by the vast interpatient diversity of ALL[7] and intra-patient oligoclonality.[8] Inhibition of a single driver pathway is unlikely sufficient for cure.[9]

We have, however, newer modalities, such as inotuzumab,[10,11] blinatumomab,[12,13]and chimeric antigen rearranged (CAR) T-cells[14,15]that target large subsets of B-ALL. Blinatumomab has demonstrated value in relapsed B-ALL.[12,13] Emerging experience has shown that blinatumomab and CAR T-cells work better at lower disease burdens.[14-17] In 2017, blinatumomab was licensed for children and adults with B-ALL in 1^{st} or second remission with measurable residual disease > 0.1%.[18]

The presence of 25% marrow lymphoblasts blasts has long been the threshold for clinical marrow relapse. [19] Earlier reports showed that early detection of overt clinical relapse provides no clinical benefit.[20,21] However, treatment fails, i.e., blast proliferation exceeds blast kill, prior to clinical relapse. We now have reliable technologies to identify low levels of re-appearing leukemia.[22] Serial assessment of MRD and prompt intervention has yet to be tested systematically.

In B-ALL, flow cytometry has largely overcome our inability to distinguish lymphoblasts from hematogones and recovery myeloblasts. Current flow cytometric or polymerase chain reaction technologies allows reliable detection of re-appearing lymphoblasts at levels 2 $\log_{10}$ below 1%.[22] Next generation sequencing (NGS) allows detection 4 $\log_{10}$ below 1% and restaging of some patients called mistakenly classified MRD positive because of low numbers of low specificity targets.[23] A new international consensus proposes that the confirmed presence of 1% lymphoblasts after the third month of therapy constitutes relapse or induction failure, if not preceded by a remission.[24]Flow cytometry, PCR, NGS, FISH, cytogenetics, and /or RT-PCR when relevant may be employed.

Reappearance of MRD greater than some number predicts relapse in adult[25] and pediatric trials.[26]Cheng et al report that reappearance of MRD reliably predicted relapse in their 30 patient cohort.[27]

Early intervention may have clinical value. Wang et al reported on 1030 children who achieved MRD negative remission. One hundred fifty had MRD reappearance at a median time of 11 months. At 5 years, the EFS was 88.5% for continuously negative MRD and 38.4% for reemergent MRD. Eighty-five MRD reemergent patients subsequently relapsed at a median of 4.1 months. Reappearance of MRD was the most powerful adverse prognostic factor in multivariate analyses. An MRD cutoff of 0.15% gave the best discrimination. After reemergent MRD, 113 continued chemotherapy at their families' choice and 37 underwent HSCT in CR1. The 2-year overall survival was 89% for HSCT and 46% for continued chemotherapy ($p< 0.001$); the cumulative incidence of relapse was 23% and 64% ($p< 0.001$).[28]

MRD surveillance is not yet standard in pediatric ALL. However, MRD surveillance is already included in adult ALL guidelines.[29,30] "Bone marrow aspirate can be considered as clinically indicated at a frequency of up to 3 to 6 months for at least 5 years." [30]

In the past marrow sampling has been required as marrow and peripheral blood are unpredictably discordant in B-ALL. [31] Marrow aspiration is painful, and children often receive anesthesia. Marrow aspirates include a variable proportion of peripheral blood affecting the precision of MRD estimates. NGS may allow peripheral blood sampling.

NGS has further lowered the limits of quantification to 10^{-6} and raised the possibility of peripheral blood monitoring in B-ALL.[31] Rau et al found that end induction peripheral blood (PB) NGS was positive in nearly all cases marrow MRD by flow was positive at 0.01%. Muffly et al found that clinical relapse followed reappearance of peripheral blood NGS with a median of 90 days after HSCT and 60 days following CAR T therapy. Peripheral blood NGS surveillance of higher risk B-ALL patients seems worthy of investigation.

Clinical features, molecular features, and response to therapy allow us to identify patients at greater or lesser risk of relapse.[32] The adolescent and young adult population seems apt for a trial of such a strategy. Favorable cytogenetics are uncommon, and the marrow relapse rate is substantial.[33] The burden of current therapy is already extreme and the efficacy of conventional salvage therapy poor.[12]

Estimating a 20% relapse rate between 10 months and 36 months and q3month sampling, 8/10 patients would have 72 negative assays, and two relapsing patients might have 9 assays, for a total of 81 assays with about 1/40 being positive.

Serial PB sampling adds little to the burden of treatment. Detection of confirmed treatment failure at an MRD level, allows immediate use of blinatumomab or CAR T-cells with a high probability to proceed to transplant MRD negative. Another round of toxic cytotoxic chemotherapy, much like the therapy that already failed, might be avoided. "If not now, when."

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