Medicina de precisión en leucemia linfoblástica aguda

Precision medicine in acute lymphoblastic leukemia.

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Contemporary minimal residual disease-directed therapy and supportive care have increased 5-year survival rate of childhood acute lymphoblastic leukemia (ALL) to more than 90%[1]. With effective systemic and intrathecal therapy, prophylactic cranial irradiation can be omitted in all patients, regardless of their presenting features[2]. In a meta-analysis of aggregate data of 16,623 patients treated between 1996 and 2007 by 10 cooperative study groups, none of the subgroups of patients with B- or T-ALL benefitted from prophylactic cranial irradiation[3].

Recent studies showed that the optimal incorporation of minimal residual disease (MRD) monitoring into treatment strategies should take into consideration not only the level and the timing of measurement but also the genetic subtype of leukemia as well as treatment intensity and components before and after the MRD determination[4,5]. Despite response-adapted treatment, MRD levels remain to have prognostic significance[6]. Depending on the protocol design, MRD level has been measured during day 8 and day 15/19 of remission induction, upon completion of 4 to 6 weeks (day 29, 33 or 42) of remission induction, and at the end of consolidation treatment (day 78, week 14, or week 15)[4,5]. Negative MRD during the first two weeks of remission induction with only 3 or 4 drugs would help to identify very low risk patients for treatment reduction. In our Total Therapy study XV, patients with t(12;21)/*ETV6-RUNX1* or hy-

perdiploidy >50 ALL and a negative MRD finding on day 19 of remission induction had a particularly low risk of relapse (1.9% and 3.8%, respectively) and are excellent candidates for treatment induction[7]. By contrast, positive MRD at the latter time points of treatment (e.g., at the end of remission induction after treatment with 7 or more drugs and especially after consolidation treatment) should be useful to identify patients who have a high risk of relapse and require more intensive or novel therapy for cure[6,7].

To date, many leukemia therapists would consider patients with unfavorable genetic or immunophenotypic feature [e.g., Philadelphia chromosome (Ph)-positive, Ph-like, low-hypodiploid, near-haploid, t(17;19) with *TCF3-HLF* fusion, t(4;11) with *MLL-AF4* fusion, or intrachromosomal amplication of chromosome 21] and high levels of MRD at the end of remission induction or persistent disease after consolidation treatment, to be suitable candidates for allogeneic hematopoietic cell transplantation[1,4]. However, recent studies showed that effective post-remission treatment can lessen or even abolish the adverse prognosis of high levels of MRD in certain subtypes of ALL. In this regard, recent studies suggested that post-remission chemotherapy, such as consolidation treatment phase IB of AIEOP-BFM regimen with 2 courses of cyclophosphamide, mercaptopurine and cytarabine, might be effective in reducing MRD and mitigate adverse prognosis of early T-cell precursor ALL, once considered very high risk leukemia and candidate for hematopoietic cell transplantation[8,9]. Similarly, in an intergroup collaborative study, many children with hyperdiploid>50 ALL and induction failure with 5% or more blasts at the end of remission induction were rescued by consolidation treatment with high-dose methotrexate and mercaptopurine and were spared from allogeneic hematopoietic cell transplantation[10]. Hence, treatment approach must be implemented within a refined risk stratification schema based on leukemia subtype and minimal residual levels measured in 2 to 3 time points, as well as available treatment. It should be noted that sequential MRD measurements beyond remission induction phase were informative only in patients who had detectable MRD at the end of remission induction; chemotherapy could cure patients with decreasing MRD post-remission while those with increasing MRD required intensive alternative therapy followed by immuno-cellular therapy[6]. By contrast, routine sequential monitoring of MRD was not useful in patients who attained negative MRD status at the end of remission induction because the vast majority of subsequent tests were negative, and early detection of re-emergence of MRD did not improve outcome[6].

With the advent of genome-wide analysis and especially next generation sequencing, all cases of ALL can now be classified according to their specific driver genetic mutations, increasing number of which are now amendable to targeted therapeutics[1]. In this regard, ABL tyrosine kinase inhibitors and JAK inhibitors promise to improve outcome of Ph-like ALL or T-cell ALL with ABL-class fusion transcript, and those with genetic lesions involving JAK-STAT pathway, respectively[11]. Novel therapies under investigation that may serve as bridge therapy for allogeneic hematopoietic cell transplantation include venetoclax, inotuzumab, denintuzumab, ofatumumab, and obinutuzumab. For cases without targetable lesion, bortezomib or clofarabine in combination with other agents may also be used as bridge therapy[1]. Early results with autologous CAR T cell therapy have generated impressive results in patients with relapsed and refractory B-ALL, even among those who had failed allogeneic transplantation with overt leukemia[12]. Interestingly, CAR T cell therapy appeared to eradicate central-nervous-system leukemia without the need of cranial irradiation, and cure patients with bone marrow disease without allogeneic transplantation[13]. Improved supportive care has made many of the side effects of CAR T cell therapy, such as cytokine-release syndrome, neuropathy, tumor lysis syndrome, and B-cell aplasia manageable[14].

Declaración de conflictos de interés:
El autor declara que no posee conflictos de interés.

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