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Minimal residual disease: Evolution of technology and clinical impact

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By definition, minimal residual disease (MRD) is the persistence of leukemic cells after chemotherapy at numbers below the sensitivity detection level of routine morphology. MRD is the strongest prognostic parameter, guides treatment decisions and can be used as a surrogate end point in clinical trials.

Molecular based methods: In lymphoid malignancies, the concept of MRD detection relies on the fact that each case has a unique immune receptor gene rearrangement. The consensus primer PCR-based approach has low sensitivity (0.5-0.1%) and oligoclonality is a limiting factor. While the classical most widely used ASO-PCR method with 10^{-5}-10^{-6} sensitivity is time-consuming and labor intensive. In myeloid malignancies, Q-real-time PCR is used for cases with fusion gene rearrangements mainly in CML and M3.

Flow cytometry-based methods: Flow cytometry MRD detection relies on the fact that leukemic cells do not obey the rules of normal differentiation. This forms the basis of leukemia-associated immunophenotype (LAIP). For ALL, it is the method of choice in most centers and used to make treatment decisions especially in pediatric ALL. For AML, an informative LAIP may not be recognized in a substantial number of cases and the approach of "different from normal pattern" or leukemia stem cell markers may be used for MRD detection. Flow cytometry is rapid and reliable but the sensitivity is questionable.

High-throughput technologies: These were introduced to overcome the limitations of the time consuming labor intensive molecular techniques and the questionable sensitivity of standard flow cytometry. These are high throughput sequencing and multidimensional next-generation flow cytometry.

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Adult acute lymphoblastic leukemia biology: A gate towards cure

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Acute lymphoblastic leukemia (ALL) is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development. Leukemic cells accumulate relentlessly because of their altered response to growth and death signals. While ALL is mostly curable in children, similar progress in the treatment of ALL in adults has lagged behind with some patients suffer from refractory or recurrent disease and cannot be cured with conventional chemotherapy. The established prognostic factors include tumor burden, immunophenotype, cytogenetic findings, molecular genetics and early minimal residual disease detection. However, the need to improve treatment results drove researchers' efforts to extrapolate more prognosis controlling factors, to unravel new ones and to present novel therapeutic drugs. Recently, understanding of disease biology paved the way towards novel personalized therapeutic approaches.

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