Paediatric Acute Lymphoblastic Leukaemia (ALL)

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Acute lymphoblastic leukaemia (ALL) is the most frequent malignant disease in childhood and adolescence, with an annual incidence of approximately 3–4 cases per 100,000 children under 15 years of age. Multimodal chemotherapy forms the base of current ALL treatment. Based on excellent national and international collaboration in consecutive prospective, randomized clinical trials, the prognosis of childhood ALL has significantly improved over time. Currently, up to 90% of all paediatric patients with ALL will survive.

However, 15–20% of ALL patients eventually develop disease relapse. Of these patients, 60–80% will achieve a second complete remission (CR) with intensive chemotherapy regimens. Despite this high probability of obtaining a second CR, patients with early bone marrow relapse (namely those occurring within 30 months from diagnosis) have a poor prognosis even if allogeneic stem cell transplantation (allo-SCT) is used as consolidation therapy (Locatelli et al. 2012). According to data from the Berlin-Frankfurt-Münster Group (BFM), patients can be grouped (S1, S2, S3, and S4) according to the site of relapse, immune phenotype, and the time interval between diagnosis and relapse. In S3 and S4 patients, prognosis is worse compared to S1/S2 children, with survival rates of only 25%–30% in the whole

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cohort of patients (von Stackelberg et al. 2011) and most recently 65% and 69% in patients who achieved remission and could receive a transplant from a matched donor (Peters et al. 2021).

In high-risk patients in CR 1 or in relapsed patients with low-risk profiles (CR2, S2), conventional chemotherapy followed by allo-SCT can cure up to 80% of patients (Peters et al. 2015, 2021). In contrast, in patients who relapse after allo-SCT, long-term survival is unlikely, and only 15% of these patients will survive the disease (Kuhlen et al. 2018). Thus far, long-term survival is only possible through a second allo-SCT if patients can obtain an additional CR and are fit enough to receive a second transplant. Second allo-SCT carries a considerable rate of toxicity and mortality, and treatment lasts approximately 6–8 months; finally, approximately 30% of these patients survive (Yaniv et al. 2018).

Thus, there is an unmet medical need among children and adolescents who have the following conditions:

- Primary refractory ALL,
- Treatment refractory relapsed ALL,
- A second relapse of their ALL, or
- Patients who relapse after allogeneic SCT and
- Patients with very high-risk ALL who should undergo allo-SCT but are not eligible for the procedure for medical reasons.

Consequently, with the introduction of CD-19-directed CAR-T cell therapies, these patients are candidates for clinical studies and finally for licencing trials of different CAR-T cell products (Maude et al. 2018). For this patient group up to the age of 25 years, one CAR-T cell product is currently approved by the FDA and EMA. Children, adolescents, and young adults belonging to one of the abovementioned patient groups have an indication for treatment with CAR-T cell therapies. Whether these are the right candidates who benefit most from the novel treatment options remains to be demonstrated. Prospective studies are planned, and a few have already begun to investigate whether the best benefit of CAR-T cell treatment can be obtained if patients were treated early in the course of the disease.

Key Points

- Patients with ALL in the second relapse, with refractory disease or who relapse after allo-SCT may be considered for CD19 CAR-T cell therapy.
- Effective lymphodepleting chemotherapy is needed to allow expansion of CAR-T cells.
- The level of measurable residual disease (MRD) seems to be correlated with response and durable remission.

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