Adult Acute Lymphoblastic Leukaemia

11

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ALL is a malignancy of lymphoid progenitor cells, with a bimodal incidence, peaking in early childhood and in older age. In children, ALL tends to have an excellent prognosis, with more than 85% of patients achieving long-term survival. The outcome of younger adults has improved considerably as well. However, overall survival decreases with age (Dores et al. 2012), partially due to the different genetic background of adult ALL, with a higher proportion of Philadelphia chromosome-positive (Ph+) ALL and Ph-like and KMT2A rearrangements in comparison to childhood ALL (Iacobucci and Mullighan 2017). The introduction of paediatric-inspired regimens has improved outcomes in adults, but these regimens are less tolerated in older patients (Curran and Stock 2015).

The standard upfront therapy for ALL includes corticosteroids, multiagent chemotherapy, antimetabolite therapy, and intrathecal therapy. Following induction, consolidation and maintenance therapy are initiated. In high-risk cases, allogeneic haematopoietic stem-cell transplantation (allo-HSCT) is considered during the first remission. Adults with relapsed ALL have a poor chance of achieving remission with chemotherapy (Frey and Luger 2015). Novel agents, such as inotuzumab ozogamicin, an antibody–drug conjugate targeting CD22, and blinatumomab, a bispecific engager targeting CD19 and CD3, improve remission rates, but overall survival remains poor (Kantarjian et al. 2016, 2017). Relapse therapy is usually followed by allo-HSCT if not performed earlier. ALL cases refractory to two or more lines of therapy can be considered for CAR-T cell therapy.

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CAR-T Cell Therapy for Adult ALL

Currently, in 2021, no regulatory agency has approved a CAR-T cell product for adult ALL patients above 25 years of age. Young adults aged 18–25 were included in the pivotal ELIANA study and are eligible for tisagenlecleucel (Maude et al. 2018). Other single-institutional studies also included young adults in a paediatric-focused study. Only a few groups have reported clinical trials in adults with ALL (Table 11.1). Most trials include small patient numbers, usually younger adults, and may represent selected patient populations. Remission rates across trials are high, with more than 70% of patients achieving complete remission, regardless of cytogenetic background, prior therapies and age. Occasionally, response rates are reported as intent-to-treat, referring to all included patients in contrast to only those receiving CAR-T cell therapy.

Toxicity has been a significant issue in all trials, and fractionation of the dose by administration of a partial dose on Day 0 and the remainder after several days was shown to be safer (Frey et al. 2019; Park et al. 2018). Several groups also administered lower doses to patients with a high disease burden to prevent toxicity (Roddie et al. 2020). Alternative approaches to enhance safety include earlier administration of tocilizumab and low-dose steroids (Gardner et al. 2019; Kadauke et al. 2021; Liu et al. 2020). Using a novel low affinity CD19 CAR-T cell was also associated with lower toxicity (Ghorashian et al. 2019; Roddie et al. 2020).

The prognostic factors that are associated with higher remission rates and better outcome in adult ALL include lower disease burden, as assessed by the blast count in bone marrow; lower LDH; and higher platelet count prior to lymphodepletion (Hay et al. 2019; Park et al. 2018). Due to the time delay between the detection of relapse and infusion of CAR-T cells, in many cases, it is necessary to deliver bridging therapy. The optimal regimens need to be defined.

Assessing the leukaemia burden before CAR-T-infusion and after potential bridging therapies is recommended because the outcome of patients with a high disease burden is inferior to that of those without persistent disease or minimal residual disease (MRD) only. The results may be inferior in ALL patients previously treated with blinatumomab (Pillai et al. 2019), although this may represent a selection of more resistant patients. TP53 mutations were associated with a worse outcome. Additionally, conditioning with fludarabine and cyclophosphamide was superior to cyclophosphamide alone in adults, similar to findings in children.

Many trials report MRD status determined by flow cytometry post CAR-T cell therapy, showing that almost all remissions are (based on flow-cytometry) MRD negative. Molecular detection of MRD via PCR or next-generation sequencing (NGS) is more sensitive, and NGS-MRD negativity after CAR-T cells has been shown to be associated with an improved long-term outcome (Hay et al. 2019).

Table 11.1 Clinical trials reporting the outcome of adult ALL treated with CAR-T cells

Group	*n*	LD	Construct	Dose	CR (%)	MRD neg of CR	Consolidative therapy	Comments
U. Penn (Frey et al.)	35	Cy (300 × 6, *n* = 25), Flu/Cy (*n* = 5), other (*n* = 3), none (*n* = 2)	FMC63-41BBz	5×10^8 single/fractionated	24 (69)	100% (flow)	9 HSCT, 15 none	2 y OS 47%; fractionation of dose is safer
FHCRC (Hay et al.)	53	Cyclophosphamide (*n* = 11) vs. flu/cy (*n* = 42)	FMC63-41BBz at CD4:CD8 prespecified ratios	2×10^5/kg (*n* = 33), 2×10^6/kg (*n* = 20)	45 (85)	100% (flow), 71% (20/28 NGS)	18 HSCT, 27 none	Low LDH and high platelet levels pre-LD improve outcome; median OS 20 months in responders
MSKCC (Park et al.)	53	Cyclophosphamide (3 g/m^2, *n* = 43), Flu/Cy (*n* = 10)	MSKCC-28z	1–3 × 10^6/kg	44 (83%)	72% (32 of 44)	17 HSCT, 26 none, 1 other	Median survival 12.9 months
Beijing (Dai et al.)	6	Flu/Cy	CD19/22 (m971/FMC63)-41BBz	1.7–3 × 10^6/kg	6 (100)	100%		3 relapsed, short follow-up time
UCL AUTO1 (Roddie et al.)	19	Flu/Cy	CAT-41BBz	10–100 × 10^6	16 (84)	100%	2 HSCT, 14 none	
Lu Daopei (Zhang et al.)	110 (39 adults)	Flu/Cy	CD19-28z (*n* = 21), CD19-41BBz (*n* = 89)	1–10 × 10^6/kg	102 (92)	94%	75 HSCT, 27 none	Worse outcome with TP53 mutations

Consolidation After CAR-T Cell Therapy

Despite durable CAR-T cells being applied as definitive therapy for relapsed ALL in children, adult data are controversial. Outcomes were not improved by allo-HSCT in patients treated with CD28-based CAR-T cells, which have short-term persistence (Park et al. 2018). In contrast, adults treated with CLT019 (Frey et al. 2019) had better outcomes if transplanted during CR after CAR-T cell therapy. Several centres recommend allo-HSCT for adult ALL patients following CAR-T cell therapy even in the presence of MRD-negative remission (Hay et al. 2019; Zhang et al. 2020; Zhao et al. 2020). Patients with molecular MRD positivity following CAR-T cell therapy, patients with rapid loss of CAR-T cells, and patients who have not received a previous HSCT are candidates for consolidative HSCT (Jacoby 2019; Jiang et al. 2020).

Relapse After CAR-T Cell Therapy

Relapse after CAR-T cell therapy occurs in 30–50% of patients. In instances of durable CAR-T cells, there is a higher probability that relapsed ALL will not express CD19, occurring in up to 40% of cases. If CAR-T cells are lost early, CD19 expression may be preserved. A second dose of CAR-T cells led to rare responses in patients with ALL who relapsed after CAR-T cell therapy or were refractory to this treatment (Gauthier et al. 2020). Other therapies, such as novel antibody-based or CAR-T cells targeting other antigens, are optional.

Key Points

- No CAR-T cell product is approved for patients with ALL older than 25 years.
- Clinical trial data for adult ALL are limited.
- CAR-T cells appear to me more effective and tolerated better if used in the MRD setting of ALL.
- The use of consolidative HSCT after CAR-T cells in adults is still a matter of debate.

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