The role of immunotherapy in relapse/refractory precursor-B Acute Lymphoblastic Leukaemia: real life UK/Ireland experience in children and young adults

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To the editor:

Treatment of relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R B-ALL) in children remains a challenge, with only 30-50% of patients being salvaged by intensive chemotherapy and allogeneic haemopoietic stem cell transplantation (HSCT)(Schrappe *et al*, 2012), with a dismal survival for those who relapse after HSCT (Kuhlen *et al*, 2018). Results of immunotherapy with Blinatumomab or autologous/allogeneic CART cells hold out a promise of better outcomes (Maude *et al*, 2018; Ghorashian *et al*, 2019; Locatelli *et al*, 2020; Qasim *et al*, 2017) and are now moving to the front-line of treatment protocols for selected high-risk patients (AALL1721/CASSIOPEIA, NCT03876769). To guide clinicians on diagnosis and treatment for complex cases of acute leukemia, we have established a national advisory panel with a membership of all UK/Ireland paediatric and young adult haematologists that meets fortnightly and recommends best available treatment options including immunotherapy for R/R B lineage ALL. We audited how the panel's advice facilitated access to advanced immunotherapies in a "real-world" setting.

From September 2016, the panel prospectively recorded anonymous data on referred patients, including: age, underlying disease, referral questions and final panel advice. Cut-off date for data analysis was 28th February 2020. Four CAR-T clinical trials could enrol patients during this period: CARPALL (NCT02443831), AMELIA (NCT03289455), UCART19 (NCT02808442), ALLPALL (NCT04094311) and from the end of 2018 tisagenlecleucel (Kymriah) was commercially available in the UK (Ali *et al*, 2020). Follow-up details on the treatment that patients received and current status was obtained by a subsequent survey of centers.

Twenty-six paediatric haematology centers participating in the panel referred at least one patient with R/R B-ALL for advice on curative treatment. The panel database included 230 B-ALL patients, and for 138 patients (60%) the referring centre sought advice on curative treatment. Overall, the first recommended option was SCT 73/138 (53%) patients, CAR-T approach 46/138 (33%), chemotherapy 13/138 (9%), palliation 4/138 (3%) and not specified 2/138 (1%). The panel recommended antibody therapy for 47 patients (34%): (Blinatumomab for 34 patients; Inotuzumab for 8; either Blina or Ino for 5). Median age of children eligible for CAR-T was 8 years (range 0.7-16) and four patients were ≥ 18 years old (range 18-25). In this group, we observed that 31/46 (67%) patients eventually received a CAR-T product. Distribution of patients according to the product received is shown in **Fig. 1.** Of note, one patient was enrolled into NIH clinical trial using bi-specific CAR19/22 (NCT03448393), and one patient received two different CAR-T products. At the time of data analysis 73% (22/30) were alive, and 53% (16/30) remains in remission without further treatment. The main cause of death was relapse (7/9, 78%); one patient died of transplant-related complications, and another due to severe CRS. Conversely 15/46 patients (33%) could not receive CART cells despite a recommendation to pursue the option. As shown in **Table 1,** lack of available slots for trial recruitment prior to licensing of Kymriah and disease progression accounted for the majority. Overall survival was 53% (8/15) in this group, and two patients are currently awaiting CAR-T cell treatment for relapse after a transplant.

Although a survival analysis was beyond the aim of this audit, it was noteworthy that the outcomes for CART recipients in this intention-to-treat "real-world" audit were similar to those reported in clinical trials of Kymriah (Maude *et al*, 2018). Of note, immunotherapy was

highly effective in patients with KMT2A rearrangement (MLL), who normally have poor prognosis (Pieters *et al*, 2019). Of the 8 patients included in this sub-group (6%), four received blinatumomab and subsequent SCT while 2 patients received Kymriah. These six patients are currently alive and in remission. Two patients were referred to palliative care.

This analysis provides a "real-world" snapshot of how immunotherapy has been incorporated into the treatment pathway for children and young adults with relapse/refractory B-precursor ALL in UK/Ireland in the last 4 years. We observed that around a third of patients discussed were considered a suitable candidate for immunotherapy and 2/3 of those for which it was recommended could access CART therapy. The proportion increased after Kymriah received NICE approval suggesting that the main barrier to accessing it was the absence of a licensed product and we intend to monitor access through regular audits.

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Figures

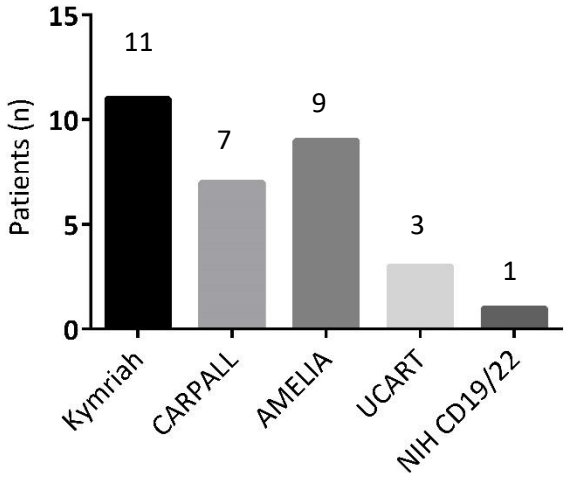

Fig.1: Distribution of patients according to the CAR-T cell product infused

Tables

Reason for not receiving CAR-T	**Patients (n)**	**Alternative treatment received**	**Survival**
No slots available	5	SCT (2/5) Carfilzomib (1/5) Inotuzumab (1/5) Chemotherapy (1/5)	4/5
Low MRD	3	DLI (1/3) Chemo+SCT (1/3) Blinatumomab (1/3)	3/3
CNS isolated relapse	1	Palliation (1/1)	0/1
CD19 neg relapse	1	Palliation (1/1)	0/1
Disease progression	4	Palliation (1/1)	0/4
Patient choice	1	Chemotherapy (1/1)	1/1
	15/46 (33%)		8/15 (53%)

Table 1: List of obstacles that prevented patients from receiving a CAR-T treatment, the alternative treatments received and survival.