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.

References


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G.O. and A.V. wrote the first and subsequent drafts of the manuscript; all authors contributed to the acquisition or analysis of data, critically revised the manuscript, and approved the final version for publication.

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Figures

![Fig.1](image.png)

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

Tables

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

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