Post-CAR-T Cell Therapy (Consolidation and Relapse): Lymphoma

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Even after a decade of use, CAR-T cell therapy for non-Hodgkin lymphoma (NHL) is still evolving, and disease control is now the main concern in the majority of experienced centres. Indeed, despite highly appealing objective response (OR) rates in refractory patients, the long-term overall survival (OS) of this population has only slightly improved. Pivotal studies have suggested that 2-year OS rates do not surpass 30%, even though results improve when complete response (CR) is achieved within the first 3 months after treatment (Wang et al. 2020; Schuster et al. 2019; Neelapu et al. 2017). Although achieving this exceptionally high level of OR is praiseworthy, similar improvements have not been made regarding OS, and current OS probabilities are not satisfactory. Of course, there are multiple reasons for this; a substantial proportion of patients either do not achieve an initial response or experience progression very soon after treatment, with poor OS (Chow et al. 2019). Both populations present with disease burden or aggressive cancer prior to CAR-T cell therapy, possibly having been referred too late in the course of treatment or waited too long before CAR-T cells were processed for them. Both of these issues have potential solutions, such as more widely publicizing the efficacy of CAR-T cells, which may increase referrals at an earlier stage, and developing methods, which are already being heavily investigated, for shortening the manufacturing process (Rafiq et al. 2020). In the latter case, the use of allogeneic lymphocytes could allow for already prepared cells to be readily used when needed and would most likely be the most efficient strategy as long as the risk of graft-versus host disease is offset (Graham and Jozwik 2018). Thus, achieving CR is a crucial step in increasing OS, as patients with partial response (PR) or stable disease (SD) present with lower OS, while currently, recurrence appears to be rare when CR is maintained for more than 6 months (Komanduri 2021). However, the disease will likely recur in more than

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half of patients in the months following treatment, possibly due to issues such as the poor persistence of CAR-T cells (which may not be as crucial as once thought for acute lymphoblastic leukaemia (Komanduri 2021)) or the loss of target antigen expression (which has been regularly documented (Rafiq et al. 2020)). Both of these mechanisms could potentially be used to develop methods that reduce recurrence after CAR-T cell therapy. In fact, the most popular approaches currently being investigated are attempting to either use two CAR-T cell types that each target different antigens or to create CAR-T cell constructs that target either multiple antigens or an antigen other than CD19 (Shah et al. 2020). The concomitant infusion of CAR-T cells with targeted therapies is also being explored in other B-cell malignancies and appears to both increase the CR rate and decrease recurrence (Gauthier et al. 2020). When recurrence does occur, patient OS is rather dismal, and the best remaining option would most likely be inclusion in a clinical trial. If this option is not available, salvage therapy may be attempted, although cytotoxic treatments are extremely limited given that most diseases have been refractory to numerous lines of treatment prior to immunotherapy. A few case reports and studies with a small patient population receiving anti-PD-1 antibodies, ibrutinib, or ImiDs have been reported with largely anecdotal supporting evidence (Byrne et al. 2019). However, even in the case of a new objective response (OR), the subsequent risk of recurrence is substantial and may invite further consolidation with allogeneic haematopoietic stem cell transplantation (Byrne et al. 2019), which has already been performed in patients treated for acute lymphoblastic leukaemia (Hay et al. 2019). However, the efficacy of this strategy remains to be validated in NHL patients in clinical trials. Further supporting evidence, although limited, has recently been reported concerning an additional treatment with CAR-T cells inducing an OR. Of the 21 NHL patients included in the study, the OR rate after the second infusion was 52% (CR, $n = 4$; PR, $n = 7$), with some durable responses inviting further investigations (Gauthier et al. 2021). Overall, with such poor outcomes after recurrence, current efforts are also focused on predicting the patients most likely to experience disease progression and that are potential candidates for preemptive consolidation therapy, although there is no doubt that patients who do not achieve a rapid CR should be the first candidates. Additionally, immune monitoring should encompass not only CAR-T cell survival but also the detection of circulating tumour DNA (Komanduri 2021) because this could aid in detecting subclinical recurrence and in deciding whether consolidation or maintenance therapy should be administered. However, currently, all these approaches are highly speculative and require further clinical study.

Key Points

- Relapse after CAR-T cell treatment for NHL is associated with a dismal outcome.
- Presently, there is no consensus on salvage therapy.
- Investigating methods to prevent recurrence is mandatory.
- Inclusion in clinical trials is recommended.

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