Title: The implications of CAR-T cell therapy on apheresis services – a Scottish perspective

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Dear Editor,

The rapidly growing implementation of chimeric antigen receptor (CAR)-T cell therapy in clinical practice has led to a significant increase in the demand on apheresis services throughout the UK. The majority of CAR-T cell therapies rely on collection of autologous mononuclear cells (i.e. 'lymphocyte' collection). Lymphocyte collection is a time-dependent integral component necessary for treatment success, but its application can be disrupted by ongoing demands on a service ever impacted by urgent referrals in therapeutic apheresis services. Within the UK, two CAR-T cell products have been approved for commercial use (1), and more than 20 clinical trials are currently active or recruiting (2). Promising interim and long-term results suggests that this demand will continue (3–6).

In late 2019, the Scottish Medicines Consortium approved the first use of commercial CAR-T cell products for patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) in NHS Scotland (www.scottishmedicines.org.uk), with first apheresis collection performed on December 2nd, 2019. Within Scotland, currently one apheresis unit (Scottish National Blood Transfusion Services Clinical Apheresis Unit, West of Scotland Cancer Centre, Glasgow) is accredited to perform lymphocyte collection prior to CAR-T manufacturing and infusion. Between 2019 and 2020, our department had an annual workflow of 172 autologous stem cell collection procedures, 49 allogeneic donor collection procedures, 11 donor lymphocyte infusion collections, as well as routine and urgent plasma exchange, red cell exchange and extracorporeal photopheresis.

A significant challenge in delivering an apheresis service for CAR-T cell therapy is planning the 'optimal' timing for collection following referral. This is vital to ensure good quality collection with therapeutic cell doses; however, its definition remains undefined. Three clinical groups exist. Firstly, those in which malignant disease is rapidly progressive. Such patients have a limited timeframe when apheresis can safely be undertaken, often relying on bridging chemotherapy or steroids prior to apheresis, which may

impact quality and dose of collection. Secondly, those with persistent metabolic disease, requiring therapy, but not with the same degree of urgency. And thirdly, those patients at high-risk of relapse following salvage chemotherapy who may benefit from CAR-T cell therapy at a future undetermined date. In this third group, apheresis can be performed with cryopreservation of the cells which are then thawed for manufacturing (7). The acceptable duration of storage is validated up to 9 months (as per the manufacturer), therefore risk stratification of patients is crucial. There does, however, remain a paucity of data to guide when collection should occur for cryopreservation. It is infeasible and, in the current economic setting, unjustifiable, to offer this service to all 'high-risk' patients.

Since the introduction of lymphocyte collection for CAR-T in Scotland (7 months), 16 patients have been referred for lymphocyte collection following multidisciplinary team (MDT) discussion (table 1). Two patients were referred for 'prophylactic' cryopreservation collections, with the remaining for immediate manufacturing. The average time to lymphocyte collection from MDT decision was 14 days (range, minus 22 days ['prophylactic'] to 29 days). One patient failed to mobilise a therapeutic dose of lymphocytes with appropriate quality. This patient was heavily pre-treated with rapidly progressive disease requiring steroid therapy prior to apheresis and had an absolute lymphocyte count of less than 0.1x10^9/L. Despite concerns regarding leukopenia in a heavily pre-treated patient group, it has been demonstrated that optimal yields meeting the targeted absolute lymphocyte count and absolute CD3+ T cell count are achieved in 77%, with minimal count achieved in 97% (8). Our experience exceeds this, with 94% (15/16 patients) achieving the targeted yield required for manufacturing. There are, however, reported manufacturing failure rates, often secondary to inadequate collection, of up to 14% in lymphomas (9,10).

Further to optimal timing, product quality is a critical source of variability in T-cell product manufacturing and this is heavily impacted by clinical characteristics. Therefore, careful multidisciplinary assessment is critical. In order to effectively institute optimal apheresis and prompt

manufacturing, close communication is key, but it is also reliant on service availability, from apheresis slots to prompt manufacturing timescales. Realistically, as demand increases, apheresis units may struggle to accommodate this, and methods must be employed to ensure that this is realised through a multidisciplinary approach. There are a number of potential strategies to streamline this emergent clinical pathway. Refinement of inclusion and exclusion criteria for CAR-T therapy, with strong links to alternative clinical trials may help select patients most likely to benefit from the product, although this understanding will only come with more long-term data and clinical experience. Close liaison between lymphoma specialists and apheresis teams, as well as timely PET imaging in high-risk patients. Earlier recognition of high-risk patients who may benefit from CAR-T cell therapy may allow more timely planning of collections, however, the practice of 'prophylactic' collection is unlikely to be sustainable or efficient. Perhaps most crucial of all is a clear need to increase funding and allow expansion of accredited facilities to enable this critical service to be staffed appropriately.

Within Scotland, we have successfully implemented a structure to provide timely apheresis for CAR-T manufacturing. However, the challenges of undefined optimal timings for lymphocyte collection, coupled with competing demands on service provision will mean that this process will need to be continually reviewed and refined to allow for its inevitable expansion.

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