CHIMERIC ANTIGEN RECEPTOR T CELLS

A briefing document for Chief Pharmacists

Issued by: The ATMP Working Party – a subgroup of the Pharmaceutical QA Committee

December 2017

The first stop for professional medicines advice

CHIMERIC ANTIGEN RECEPTOR T CELLS (CAR-T cells).

Background

Chimeric antigen receptor T cells, so-called CAR-T, are the leading anti-cancer cell therapy in the world at present. These are regulated as medicines in the EU, specifically as somatic cell therapy Advanced Therapy Medicinal Products (ATMPs). CAR-T are generally patient-specific (autologous) cell therapies and consist of the patient's own T lymphocytes which are genetically modified to express a chimeric antigen receptor to confer antigen specificity. The genetic modification is conducted by the manufacturer using a viral vector derived from a retrovirus or a lentivirus which carries the new payload gene for the chimeric receptor.

CAR-T have been in development at multiple academic centres for over 15 years and multiple iterations have been developed and tested. Current commercial CAR-T available from Novartis (Kymriah) and Gilead (Yescarta) are both "second generation" CAR-T in which the payload in the lentivirus consists of an antibody binding site specific to CD19 plus a T cell co-stimulatory domain and an intracellular domain to initiate signalling in the T cell. The CAR-T cells all carry the same receptor so, unlike conventional T cells, they are all specific for the same antigen. These products have been licensed in the USA during 2017 and are expected to be receiving central EU authorisation during 2018.

At present the two commercial CAR-T both target the CD19 antigen which is expressed on all B lymphocytes and B lymphocyte precursors. This means they target B cell tumours such as B-ALL and many B cell lymphomas. However, many other tumour antigens are being targeted by novel CAR-T in numerous clinical trials although they are predominantly targeted to haematological malignancies at present due to difficulties in delivering CAR-T into solid tumours.

Hospital pharmacists are likely to be faced with CAR-T as licensed medicines in the near future but should also be prepared to support commercial and academic clinical trials of novel CAR-T and this briefing document aims to address all scenarios.

Guidance for hospital pharmacies –

1. **Procurement of starting materials**: As with all patient-specific ATMPs, the medicine manufacturing process begins with procurement of the patient cells from which the ATMP is to be made. Procurement, contrary to the usual pharmacy understanding where it relates to purchasing, is a clinical process which requires pharmacy oversight in order to ensure that the quality of the ATMP to be manufactured in not compromised. This is a new role for Pharmacy. In the case of CAR-T this starting material is usually a clinical apheresate derived from an apheresis machine. Procurement of human cells for manufacture of ATMPs requires a licence in the EU and may occur under a Human Tissue Authority (HTA) licence for procurement or an MHRA Blood Establishment licence. Typically hospitals perform these collections under HTA licensing within their on-site clinical apheresis facility run by the Haematology Department. ADVICE – the Chief Pharmacist should ensure that:

    a. Procurement leading to the manufacture of an ATMP will be performed under a relevant licence and that the screening of the patient for statutory infectious disease markers is

performed on a blood sample taken from the patient ON THE DAY OF PROCUREMENT. This is essential and often missed by the Haematology apheresis service since routine stem cell transplant patients are screened for infectious diseases up to 30 days prior to procurement under a unique derogation from the HTA Directions.

b. There is a secure supply chain under Pharmacy governance to ensure linkage of the donor material to the final product throughout the manufacturing process. This is essential since the patients are lymphodepleted prior to infusion of CAR-T so a mismatched CAR-T product will cause a fatal transfusion graft versus host disease (GvHD) reaction if administered. This linkage is particularly challenging in commercial CAR-T provision where the manufacture and release of drug product is likely to occur in a central facility in the US where multiple products are in manufacture simultaneously.

2. **Receipt of the drug product:** All CAR-T products will be supplied frozen at cryogenic temperatures; typically below -155^{o}C in vapour phase nitrogen (VPN). They are likely to arrive in dry shippers which are the size of a small domestic dustbin and will require secure storage in a moderately well ventilated space. Hospital pharmacists need reassuring about the risk of VPN storage and a “code of safe practice” should be drafted for circulation to alleviate unnecessary fears. The ATMP Working Party will draft an exemplar code as a workstream for 2018. Pharmacists will need to be familiar with temperature monitors attached to dry shippers of which there is a variety and satisfy themselves that they have the hardware and software to interrogate them to gather the data they need for acceptance of the product. This is routine for clinical trials pharmacists but will need to be introduced to routine practice as marketed ATMPs come into use.

3. **Pre-infusion patient treatment**: Most CAR-T are given in the setting of lymphodepletion which is typically achieved with conventional course of fludarabine over the five days prior to infusion. Most prescribing physicians will require confirmation that the CAR-T product is in Pharmacy prior to commencement of conditioning chemotherapy. It is good practice to have a check box on the form requesting dispensing of the fludarabine for confirmation that the CAR-T product has been received by Pharmacy and is suitable for issue. This should include confirmation that the expiry date of the dry shipper exceeds the duration of fludarabine conditioning.

4. **Issue of drug product**: Hospital pharmacists should issue the ATMP, however unlike any other medicine the product is specific for one patient and therefore additional supply chain precautions are necessary. A preparation step will be required. Depending on the post- defrost shelf life which is specified by the manufacturer it may be necessary to deliver the product in the dry shipper to the clinical area for local thawing and immediate infusion or if shelf-life permits this can be performed within the pharmacy and presented ready to administer to the clinical area. Pharmacists must be aware that this is a live human product so maintenance of cell viability is essential. Pharmacies should be equipped with suitable equipment e.g. blood warming equipment for rapid thawing of cryogenic bags of CAR-T, these may be required at the patient bedside. Non touch aseptic technique is essential and training will need to be

provided to staff carrying out this procedure. It is likely the administration of CAR-T products will be restricted to hospitals with an autologous haematopoietic stem cell transplant service and pharmacists are advised to liaise with these colleagues for advice on establishment of a shared service provision. Pharmacy oversight is essential as detailed in "The role of Pharmacy in the Successful Delivery of ATMPs – information for Chief Pharmacists" published in February 2017 by the ATMP Working Party – a subgroup of the NHS Pharmaceutical QA Committee. A system to ensure robust accountability is critical with each member of the supply chain being trained and competent. CAR-T are genetically modified cell therapies but the vectors used are unable to replicate in the host cells and are thus safe to be administered on a hospital ward. There is no risk to the clinical staff other than that of a conventional blood transfusion.

5. **Post-infusion care**: CAR-T cells are autologous T cells with the ability to proliferate logarithmically in vivo. They will secrete an array of inflammatory cytokines and may also induce tumour lysis syndrome. CAR-T will only be administered by clinical teams expert in the monitoring and recognition of early symptoms of cytokine release syndrome and tumour lysis syndrome and the clinical pharmacist linked to the team must ensure that appropriate therapies such as steroids and anti-IL6 agents such as Tocilizumab are available. These medicines should be held in the hospital pharmacy wherever CAR-T are to be used.

The above briefing has been written on behalf of the ATMP Working party by

Professor Mark W Lowdell, BSc (Hons), MSc, PhD, FRCPath, FRSB
Director of Cell Therapy & tQP, Royal Free London NHS FT
Professor of Cell & Tissue Therapy University College London

Professor Lowdell is a member of the ATMP Working Party which is an NHS Pharmaceutical QA Committee Subgroup.

For Further information please contact the Chair of the Group whose contact details are given below:

Anne Black
Regional QA Specialist Pharmacist – NE and N Cumbria
Chair - ATMP Working Party
Email: anne.black7@nhs.net
Tel: 0191 2820387

NHS Specialist Pharmacy Service

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