Supportive Medicines Recommended for Adults Receiving Marketed Chimeric Antigen Receptor-T Cell Therapy

Pan UK Pharmacy Working Group for ATMPs

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The first stop for professional medicines advice

The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert and informed body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The Pan UK PWG for ATMPs has a clinical subgroup which identified a need for consistent clinical advice regarding supportive medicines for CAR-T cell therapy patients.

Author's Foreword

The purpose of this document is to provide guidance on the use of appropriate supportive medicines to advise and to standardise the management of CAR-T cell patients across the UK.

This guidance document has been produced by representatives of the Pan UK PWG for ATMPs which convened in order to provide exemplar documents for the key steps in the delivery of ATMPs.

This is a consensus guideline developed with input from pharmacists of the Clinical subgroup, which includes members from the first and second wave CAR-T centres. Thank you to all who have supported the development of this document.

Please contact the author of this document with any questions:

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Supportive Medicines Recommended for Adults Receiving Marketed (Licensed) Chimeric Antigen Receptor-T (CAR-T) Cell Therapy

Introduction

Chimeric antigen receptor-T (CAR-T) cells are a novel class of systemic anti-cancer therapy in which autologous or allogeneic T cells are engineered to express a CAR targeting a membrane antigen. In the UK there are licensed CAR-T products approved to treat different relapsed/refractory lymphomas. These are tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®) and anti-CD19-transduced CD3+ cells (Tecartus®). These three products are genetically engineered autologous CAR-T cells targeting CD19. It is expected that the availability of licensed CAR-T products and new indications will increase and these guidelines can be applied to future products where clinically appropriate.

Prior to receiving CAR-T cells, patients will receive lymphodepletion (LD). CAR-T cell therapy and LD can increase the likelihood of certain side effects and infections so supportive medicines are recommended.

Scope

These consensus recommendations, prepared by the Clinical Pharmacy subgroup of the Pan UK Pharmacy Working Group for Advanced Therapy Medicinal Products (ATMPs), relate to supportive medicines recommended for adults receiving licensed CD-19 targeted CAR-T cell products, but can also be applied to other newly licensed CAR-T cell products (e.g. BCMA targeted CARs for multiple myeloma) where clinically appropriate. These recommendations are intended as guidance only and should be used in conjunction with the manufacturer's production specifications and institutional guidance.

This guidance is to support the treatment of patients receiving marketed (licensed) CAR-T cell products. For patients participating in a CAR-T cell clinical trial, the clinical trial protocol must be followed.

Therapeutic intervention	Pan UK Pharmacy Working Group recommendation	Duration of treatment	Comments
Supportive medications alongside CAR-T cell infusion			
Prophylaxis for Tumour Lysis Syndrome [1, 2]	Low/intermediate risk: *Allopurinol 300mg orally daily + oral hydration*	Commencing on first day of LD until 10 days post CAR-T cell infusion	Patient G6PD status should be checked in all patients prior to rasburicase. Rasburicase is contraindicated in patients with G6PD deficiency. *Omit allopurinol on days rasburicase administered
	High risk: *Allopurinol + rasburicase 3mg intravenously + intravenous hydration*	Allopurinol as above* plus single dose rasburicase on day of CAR-T cell infusion (review on a daily basis if further doses needed)	
Prophylaxis for Nausea and Vomiting [3]	*Ondansetron 8mg orally twice daily* Plus	Commencing on first day of LD for 6 days	Risk of emesis for FC LD: Moderate Avoid the use of corticosteroids as anti-emetics
	Domperidone or metoclopramide 10mg orally three times a day	Commencing on first day of LD regularly for 6 days then when required	

Gastro-intestinal acid suppression	*Omeprazole 20mg orally daily* *or* *Lansoprazole 30mg orally daily*	Commencing on first day of LD until platelet count >50x10^9/L	H2 receptor antagonists can be considered as an alternative based on local institutional guidance and availability
Mouth care	*Chlorhexidine 0.2% mouthwash 10ml four times a day* or *Sodium chloride 0.9% mouthwash*	Commencing on first day of LD until neutrophil count ≥1x10^9/L	
Prevention of urothelial toxicity from cyclophosphamide [4]	Not routinely recommended		For LD regimens containing total cyclophosphamide dose >1g/m^2 or patients at high risk of urothelial toxicity consider: *Mesna intravenously 20% of cyclophosphamide dose at T=0* *Mesna orally 40% of cyclophosphamide dose at T = 2 & 6 hours on each day of cyclophosphamide*
Anti-seizure prophylaxis [2]	*Levetiracetam 500mg-750mg orally twice daily.* Prophylaxis should be considered for patients receiving products with a high risk of neurotoxicity and seizures or who have a history of seizures or central nervous system disease	Commencing on first day of LD until Day +30 then reducing to *levetiracetam 250 mg orally twice daily* for one week and then stop. If well enough to be discharged home consider reducing dose at day of discharge if no ICANS	For patients who have had seizures (including non-convulsive status) there should be a discussion with the Neurology team regarding the plan for tapering. Alternative anti-epileptics can be used on discussion with Neurology.
Menstruation suppression	*Norethisterone 5mg orally three times a day* should be considered for pre-menopausal females at risk of thrombocytopaenia	Commencing on first day of LD until platelet count >50x10^9/L	*Buserelin 150mcg/dose nasal spray 1 spray each nostril three times a day* may be considered as an alternative to norethisterone for breakthrough bleeding
Pre-medications/rescue medicines for infusion related reactions (IRRs) [5,6,7]	*Chlorphenamine 10mg intravenously 6 hourly if needed*	Pre-medication for CAR-T cell infusion/management of IRRs	Do not routinely prescribe any corticosteroids as pre-medications or to manage IRRs as they may affect the efficacy of the CAR-T cell therapy. Corticosteroids should only be given on the advice of the treating Haematology consultant
	Paracetamol 1g orally 4-6 hourly if needed	Pre-medication for CAR-T cell infusion/management of IRRs	
	Pethidine 12.5mg - 25mg intravenously 8 hourly if needed	Treatment for rigors	
Rescue medications for acute toxicities [5,6,7]	*Tocilizumab 8mg/kg (max 800mg) intravenously 8 hourly if needed.*	Prescribed as PRN in advance of CAR-T infusion	Refer to 'Medical management of acute CAR-T

	Maximum 4 doses	to be administered for treatment of CRS	toxicities' for further details see (Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice)
Anti-infective prophylaxis alongside CAR-T cell therapy			
Antiviral prophylaxis [8,9,10]	*Aciclovir 400mg orally twice daily to 800mg orally twice daily* (Dose as per institutional guidance) or *Valaciclovir 500mg orally twice daily*	Commencing on first day of LD until 1 year post CAR-T cell infusion and/or until $CD4^+$ count $>0.2x10^9/L$	
Anti-pneumocystis prophylaxis [8,9,10]	*Co-trimoxazole 480mg orally daily to 960mg orally three times a week* (Dose as per institutional guidance)	Commencing on first day of LD until 1 year post CAR-T cell infusion and/or until $CD4^+$ count $>0.2x10^9/L$	In case of co-trimoxazole allergy or cytopenias precluding use of co-trimoxazole consider: *Pentamidine inhalation 300mg once a month* or *Dapsone orally 100mg once daily* or *Atovaquone 750mg orally twice daily*
Systemic anti-fungal prophylaxis [8,9,10]	*Fluconazole 200mg orally daily* or *Posaconazole tablets 300mg orally twice a day on first day then 300mg daily thereafter* for patients with prior allogeneic stem cell transplant, prior invasive aspergillosis and those receiving corticosteroids or high risk of invasive fungal infection	Commencing on first day of LD until Day 28 post CAR-T infusion or until neutrophil count $\geq 0.5x10^9/L$, whichever is later. If using posaconazole consider switching to *fluconazole 200mg orally daily* beyond Day 28 until Day 100 if severe lymphopenia ($<0.5x\ 10^9/L$) +/- hypogammaglobulinaemia (IgG<5.0 g/L))	
Antibacterial prophylaxis [8,9,10]	Not routinely recommended		May be considered in case of prolonged neutropenia $<0.5x10^9/L$ and should be based on standard institutional practice e.g. *ciprofloxacin 250mg orally twice a day*

Hepatitis B virus prophylaxis for patients with a history of hepatitis B infection [11,12]	*Entecavir 500micrograms orally daily* *or* *Tenofovir disoproxil orally 245mg daily* (As per institutional guidance)	Commencing on first day of LD until 1 year post CAR-T infusion	All HBsAg-, HBcAb+ patients should receive HBV prophylaxis. All HBsAg+ patients should receive HBV treatment or prophylaxis as guided by Hepatology. Prior to discontinuation of prophylaxis HBV DNA should be checked.
Supportive medications to consider post CAR-T infusion			
GCSF for severe / prolonged neutropenia [8,9,13]	*GCSF* dosed as per institutional guidelines may be considered to shorten duration of severe neutropenia ($<0.5x10^9$/L)	Commencing 14 days post CAR-T infusion, or after resolution of CRS or ICANS, and continued until neutrophil count $\geq 1x10^9$/L	Avoid if patient has CRS or ICANS due to theoretical concerns regarding macrophage activation. Can consider starting earlier e.g. day +5, if patient at high infection risk, as recent data on earlier prophylactic G-CSF found no effect on immunotoxicity, CAR-T expansion or prognosis
Human normal immunoglobulins (Ig) for hypogammaglobinaemia [14]	*Intravenous Ig* *0.4 – 0.6 g/kg 3-6 weekly* modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range Or *Subcutaneous Ig* *0.1-0.15g/kg weekly*		Consider for use in accordance with current NHSE commissioning guidance for patients developing hypogammaglobinaemia associated with B-cell aplasia as a consequence of CAR-T cell therapy

Note: Drug doses may require dose amendments for patients with renal and hepatic impairment. Consult manufacturer's specifications.

FC LD = Fludarabine and cyclophosphamide lymphodepletion; G-CSF = granulocyte colony stimulating factor; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; HBV = Hepatitis B Virus; HBsAg = Hepatitis B surface antigen; HBcAb = Hepatitis B core antibody

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