



Workshop Session

Safety Considerations/ ITU Capacity

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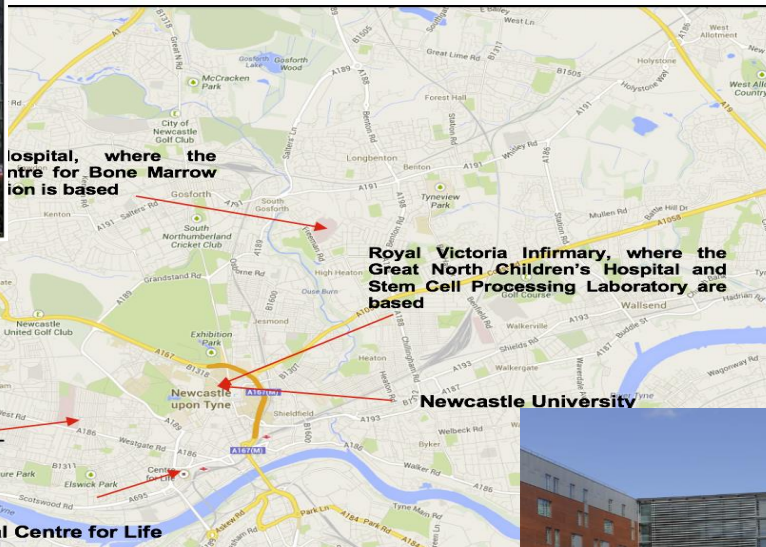
CAR-T cells

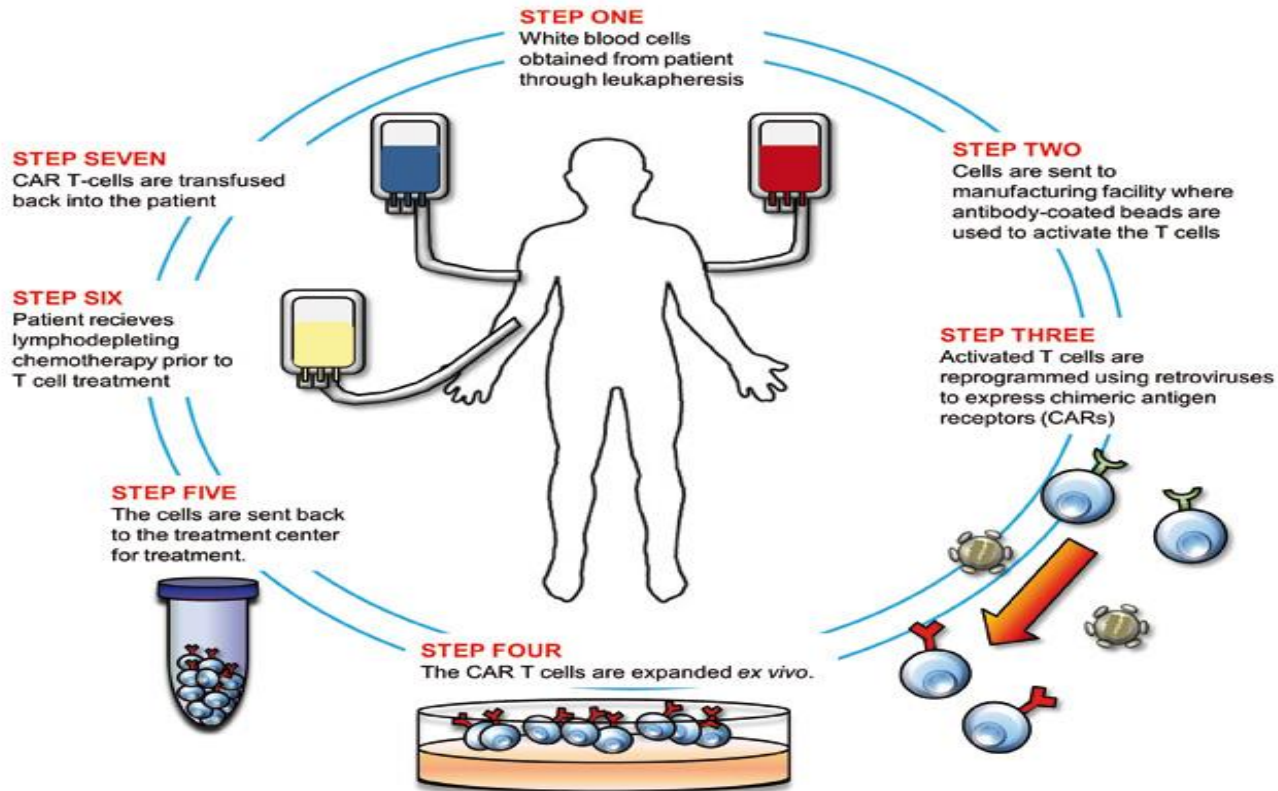
Safety considerations

Overview

- Assessment and management of toxicity
- Challenges and implications for critical care

The Newcastle upon Tyne Hospitals NHS Foundation Trust

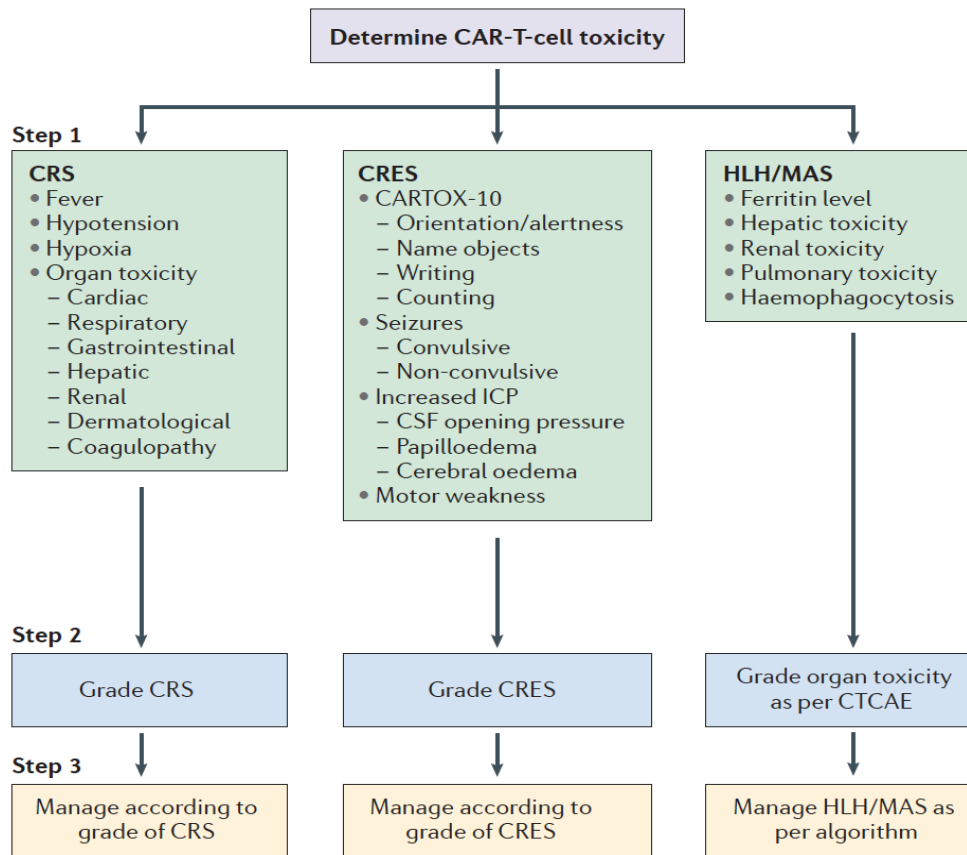




Complications of CAR-T therapy

- Cytokine release syndrome (CRS)
- CAR T cell related encephalopathy syndrome (CRES)
- HLH/MAS
- Infections secondary to lymphodepletion and B-cell aplasia

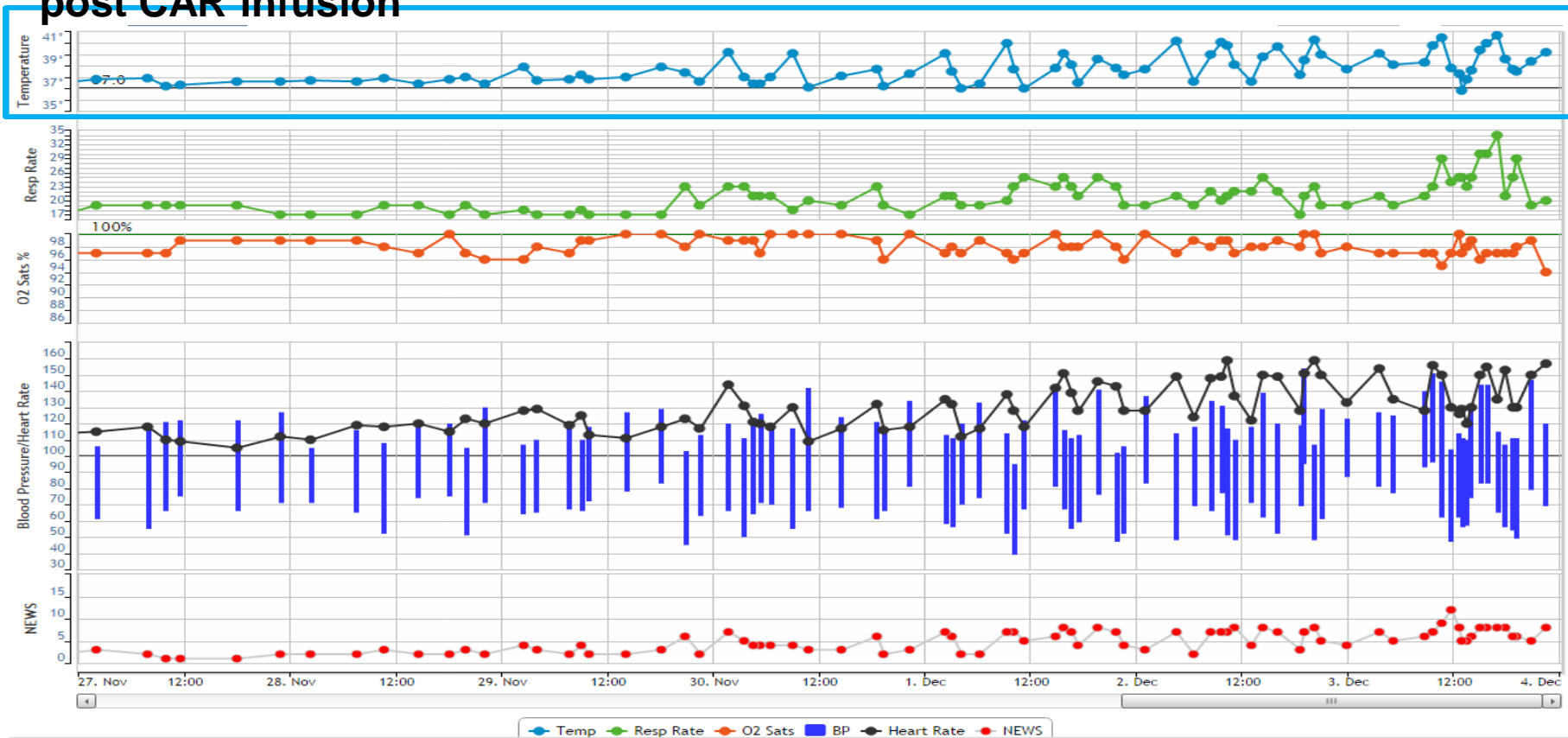
3 step approach



Cytokine release syndrome (CRS)

- Occurs in 20-40% of CAR treated patients
- Typically within the first week post infusion
- Severity related to disease burden
- Grossly elevated serum cytokines

Day 3 5 7 9 11
post CAR infusion



Neurologic:

- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial nerve palsy
- Seizures

Hepatic:

- Transaminitis
- Hyperbilirubinemia

Hematologic:

- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

Constitutional:

- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

Cardiovascular:

- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinemia
- QT prolongation

Pulmonary:

- Tachypnea
- Hypoxia

Renal:

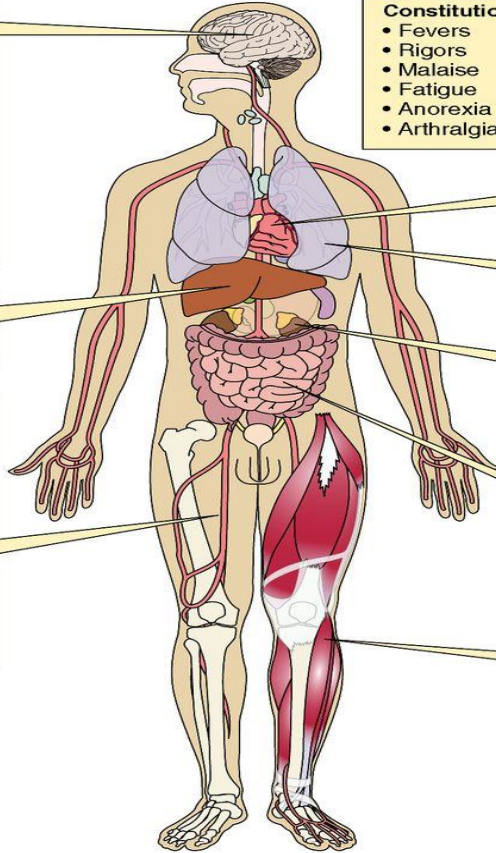
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

Gastrointestinal:

- Nausea
- Emesis
- Diarrhea

Musculoskeletal:

- Myalgias
- Elevated creatine kinase
- Weakness



Grading CRS

Symptom or sign of CRS	CRS grade 1*	CRS grade 2*	CRS grade 3*	CRS grade 4*
Vital signs				
Temperature $\geq 38^{\circ}\text{C}$ (fever)	Yes	Any	Any	Any
Systolic blood pressure $< 90\text{mmHg}$ (hypotension)	No	Responds to IV fluids or low-dose vasopressors	Needs high-dose or multiple vasopressors ⁵	Life-threatening
Needing oxygen for $\text{SaO}_2 > 90\%$ (hypoxia)	No	$\text{FI}\text{O}_2 < 40\%$	$\text{FI}\text{O}_2 \geq 40\%$	Needing ventilator support
Organ toxicities				
<ul style="list-style-type: none"> Cardiac: tachycardia, arrhythmias, heart block, low ejection fraction Respiratory: tachypnoea, pleural effusion, pulmonary oedema GI: nausea, vomiting, diarrhea Hepatic: increased serum ALT, AST, or bilirubin levels Renal: acute kidney injury (increased serum creatinine levels), decreased urine output Dermatological: rash (less common) Coagulopathy: disseminated intravascular coagulation (less common) 	Grade 1 Organ toxicities as per CTCAE v4.03	Grade 2 Organ toxicities as per CTCAE v4.03	Grade 3 Organ toxicities as per CTCAE v4.03 or grade 4 transaminitis	Grade 4 Organ toxicities as per CTCAE v4.03 except grade 4 transaminitis

Adapted from Lee et al 2014 and Delgado et al 2018; The CRS grade should be determined at least twice a day, and whenever a change in the patient's status is observed. *Grade 1 CRS can manifest as fever and/or grade 1 organ toxicity. *For grades 2,3 or 4 CRS, any one of the criteria other than fever is sufficient. †High dose vasopressors are defined as any of the following: noradrenaline $\geq 20 \mu\text{g}/\text{min}/\text{min}$; dopamine $\geq 10 \mu\text{g}/\text{kg}/\text{min}$; phenylephrine $\geq 200 \mu\text{g}/\text{min}$; adrenaline $\geq 10 \mu\text{g}/\text{min}$; if no vasopressor, vasopressin plus noradrenaline equivalent of $\geq 10 \mu\text{g}/\text{min}$; and if no vasopressor, vasopressin (not including vasopressin), noradrenaline equivalent $\geq 20 \mu\text{g}/\text{min}$. The noradrenaline equivalent dose calculator uses the VASST (vasopressin equivalent equation: noradrenaline ($\mu\text{g}/\text{minute}$)) [dopamine ($\mu\text{g}/\text{kg}/\text{minute}$)/2] + [phenylephrine ($\mu\text{g}/\text{minute}$)/10]

Management CRS Grade 1

- Supportive care, analgesia, antipyretics
- Maintain intravenous fluids
- Treat for neutropenic infections
- ECG and echo

Management CRS Grade 2

- Intravenous fluids
- **Tocilizumab early (repeat dose)**
- Low dose vasopressor SBP >90mmHg
- Low dose oxygen

Management CRS Grade 3

- Tocilizumab
- Steroids (dexamethasone 10mg IV 6 hrly)
- Organ support
- Consider infliximab (anti-TNF) and rituximab

Management CRS Grade 4

- Tocilizumab
- High dose steroids (methylprednisolone 1g/day)
- Rituximab (RQR8 'off switch')

09³⁰ Tocilizumab



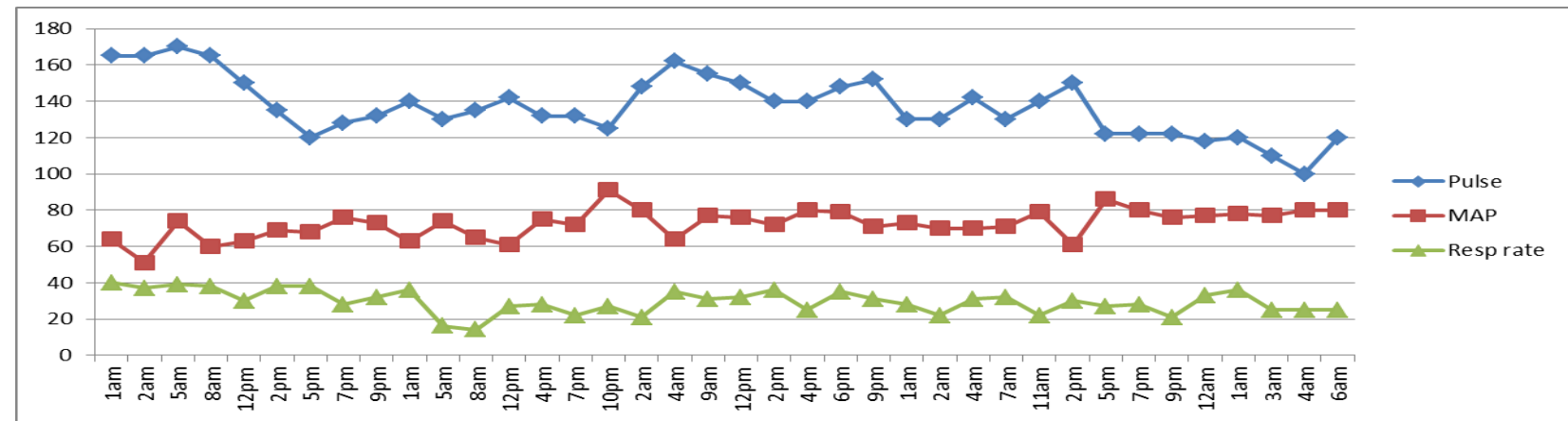
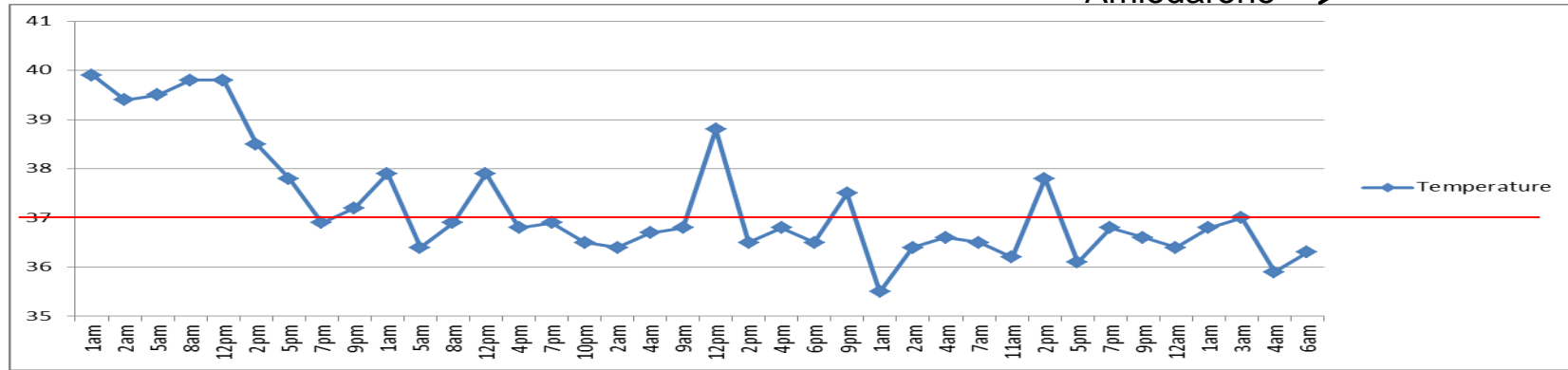
Noradrenaline

12⁰⁰ Tocilizumab
Dex x2



CPAP
Amiodarone

Dialysis Cardiac arrest 07⁰⁰



4.12.16
Day+11

5.12.16
Day+12

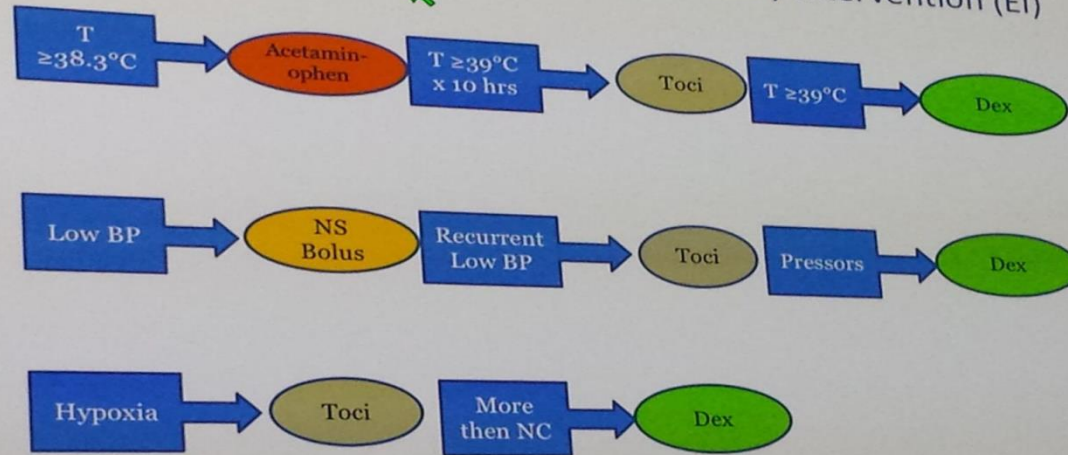
6.12.16
Day+13

7.12.16
Day+14

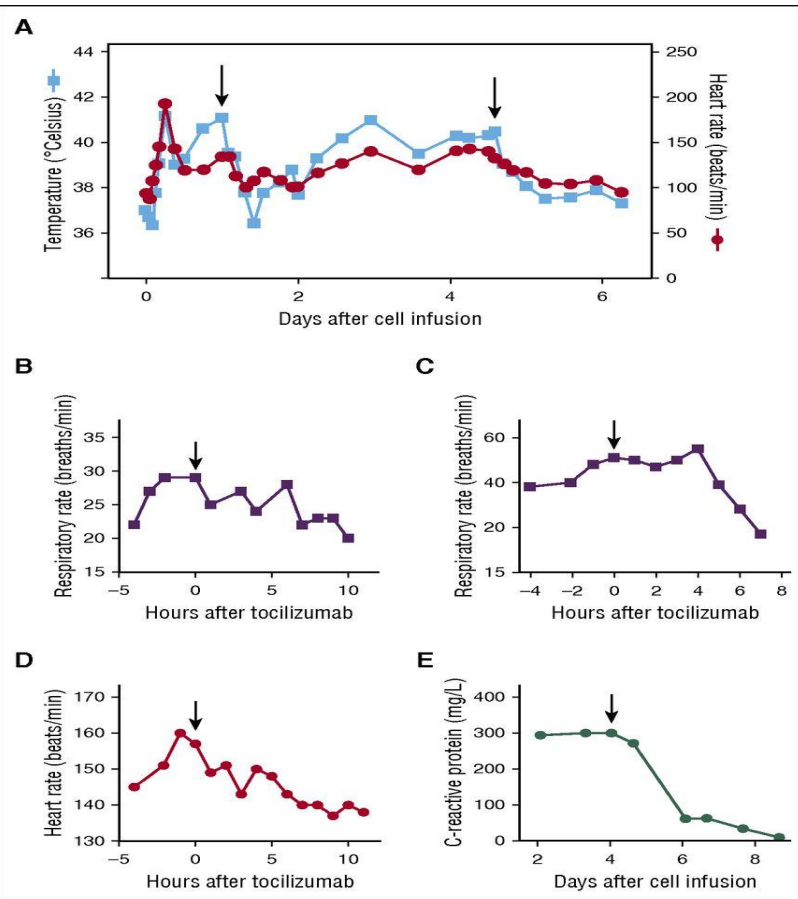
8.12.16
Day+15

Tocilizumab

PLAT-02: CRS Management Algorithm of Early Intervention (EI)



DOSING: Tocilizumab 8-12 mg/kg; Dexamethasone 5-10mg q 6-12 hours with ongoing symptoms



Neurotoxicity CRES

- Occurs in 30-40% of patients
- Biphasic presentation
- Confusion, delirium, aphasia, seizures, coma
- Pathogenesis
 - Cytokine mediated
 - CAR T-cell infiltration in brain
 - ? Cross reactivity of CD19 CAR against brain tissue

Grading CRES

Sign or Symptom	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CARTOX 10 score	10 Normal cognitive function	7 - 9 mild impairment	3 - 6 moderate impairment	0 - 2 severe impairment	In critical condition and/or cannot perform assessment
Raised intracranial pressure	NA	NA	NA	Stage 1 - 2 papilloedema or CSF opening pressure <20 mmHg	Stage 3 - 5 papilloedema or CSF opening pressure \geq 20 mmHg or cerebral oedema
Seizures or motor weakness	NA	NA	NA	Partial seizure or nonconvulsive seizures on EEG that responds to benzodiazepines	Generalized seizures, or convulsive or nonconvulsive status epilepticus or new development of motor weakness

Neurotoxicity assessment for CAR-T cell therapy

Assessment and grading of CRES using the CAR-T-cell-therapy
associated toxicity 10-point neurological assessment (CARTOX-10)
should be done at least every 8 h.

Surname	MRN
Forename	D.o.B
Address	NHS No.
Postcode	

Date									
Time									
Year (1p)									
Month (1p)									
City (1p)									
Hospital (1p)									
Prime minister (1p)									
Naming three nearby objects (max 3p)									
Writing a standard sentence (1p)									
Count backwards from 100 in tens (1p)									
CARTOX 10 score									
Raised intracranial pressure									
Seizures or motor weakness									
Neurotoxicity Grade									
Date									
Time									
Year (1p)									
Month (1p)									
City (1p)									
Hospital (1p)									
Prime minister (1p)									
Naming three nearby objects (max 3p)									
Writing a standard sentence (1p)									
Count backwards from 100 in tens (1p)									
CARTOX 10 score									
Raised intracranial pressure									
Seizures or motor weakness									
Neurotoxicity Grade									

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Management CRES Grade 1

- Neurology assessment
- Fundoscopy, CT, MRI, lumbar puncture, EEG
- Consider tocilizumab if concurrent CRS

Management CRES Grade 2

- Tocilizumab if concurrent CRS
- Steroids if refractory to tocilizumab or neurotoxicity without concurrent CRS
- Transfer ICU

Management CRES Grade 3

- Tocilizumab if concurrent CRS
- Steroids if refractory to tocilizumab or neurotoxicity without concurrent CRS
- Treat cerebral odema
- Repeat CT/MRI

Management CRES Grade 4

- High dose steroids
- Rituximab
- Treat cerebral odema and seizures
- Consider cyclophosphamide or anti-IL1 antibody

General supportive care

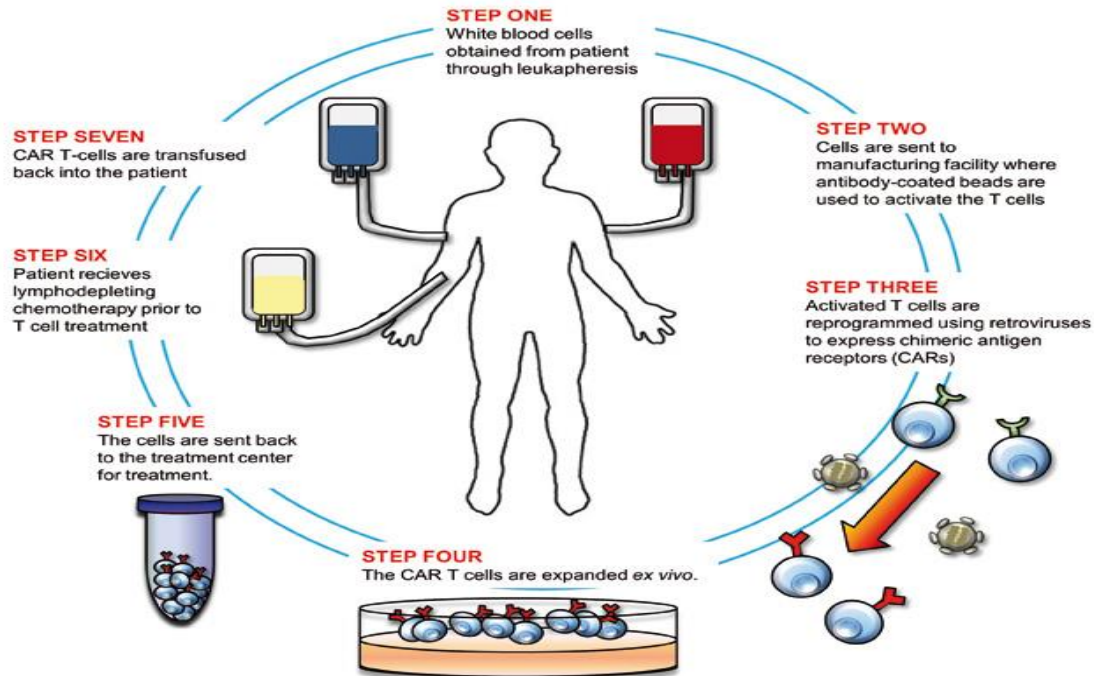
- Regular monitoring: vital signs 4hrly
- Daily bloods, weight, fluid balance
- CRS grade twice a day
- CARTOX-10 score 8 hrly

Patient follow up

- Patients stay within close proximity
- Complete daily screening for signs and symptoms of toxicity

Logistical challenges of CAR-T therapy

- Need individuals with experience and understanding of CAR T therapy
- Close interaction haematology, ICU and neurology
- Established protocols
- Rapid access to Tocilizumab
- **Expect the unexpected !**



ICU training

- Cascade training (outreach staff)
- Recognition and grading of toxicity
- Management protocols (tocilizumab)

ICU readiness

- ICU 22 beds
- MDT
 - pharmacy
 - physio
 - Microbiology
 - Outreach
- 24 hour on-call service
- Neurology review patient within few hours if neurotoxicity suspected
- Mobile EEG performed within 24 hours if required

ICU capacity considerations

- Estimating 15 patients in first year
- 20% complications needing ICU
- Length of stay 3-4 days in ICU
- Projected 12 bed days per annum (8030 bed days/yr)

Summary

- 3 stepped approach is key
- Early intervention with tocilizumab
- Multidisciplinary team approach
- Education for patients and families