Immune Effector Cell Training Workbook

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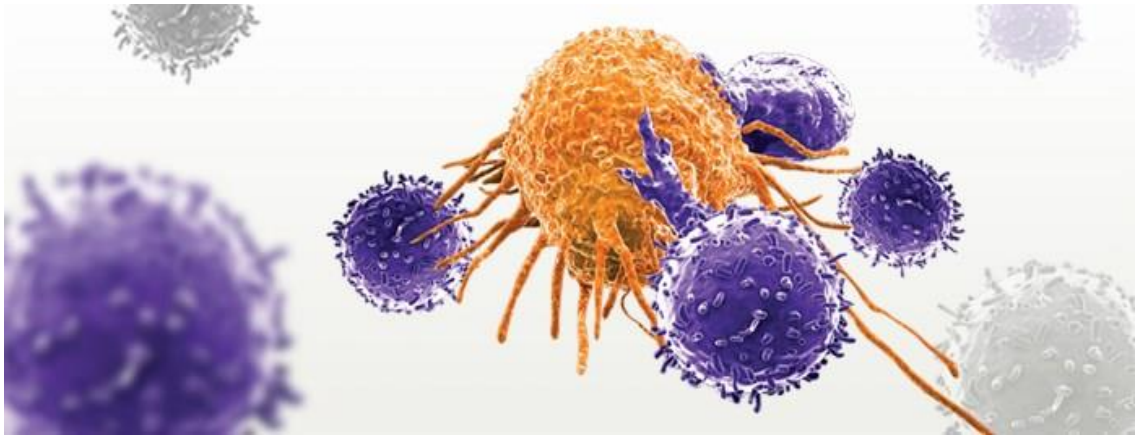
Immune Effector Cell Training Workbook



Advanced Immune and Cell Therapy Research Team.

Contents

Introduction

Welcome to the The Christie Clinical Research Facility (CRF) Immune Effector Cell (IEC) therapy workbook. This facilitated workbook has been developed for new and existing staff, caring for patients undergoing IEC therapy, usually within the context of a clinical trial. The workbook is designed to develop a clear understanding of the clinical care and processes relevant to patients undergoing IEC therapy and to support all clinical staff in developing the skills and knowledge to provide high quality care to this specialist patient group.

The workbook provides information and signposting for further independent reading on a number of key areas relevant to IEC therapy as well as an integrated list of learning objectives. The workbook and competencies are designed to complement the theoretical training which will be provided in lecture format either on The Christie specific study days, the IEC rolling education programme or self directed study through e-learning and independent reading as well as provide structure to any clinical placements undertaken.

The expected time for completion of the workbook is 4-6 months, however this timeframe is designed to be flexible depending on individuals previous knowledge and experience as well as other learning commitments. Your clinical mentor and/or the IEC practice facilitator will discuss your individual learning needs in order to personalise your training programme. A number of IEC specific standard operating procedures (SOPs) exist on Q pulse (Quality Management System) outlining specific information for many of the topics covered in this workbook and these are signposted throughout the workbook where relevant. A comprehensive list of these SOPs is also listed in Appendix A. Additionaly you will receive training and log in details on how to access Q pulse from our Quality Manager. It is your responsibility to ensure you read and are familiar with the relevant SOP's.

It is also important to read and become familiar with any trials specific teaching materials available. If you do not understand any of the information in these resources please ensure you highlight this to your assessor who can provide additional support.

Key personnel

The Advanced Immune and Cell Therapy (AICT) research team consist of a wide range of professionals from a range of backgrounds and collectively have extensive knowledge and skills to support you in caring for these patients.

Name	Role	Contact

Resources

There is a wide range of additional resources to help you in your continued professional development. These should be accessed in conjunction with the rolling education programme. A reading list and list of helpful links is included below.

Reading list

Brudno, J.N. and Kochenderfer, J. N. (2019) Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Reviews, 34, 45–55.

Brudno, J.N. and Kochenderfer, J. N. (2016) Toxicities of chimeric antigen receptor T cells: recognition and management. Blood, 127 (26) 3321-3330.

Curran, K. J. and Brentjens, R. J. (2015) Chimeric Antigen Receptor T Cells for Cancer Immunotherapy. Journal of Clinical Oncology, 33 (15) pp 1703-1706.

Gutierrez, C. et al (2018) Management of the Critically Ill Adult Chimeric Antigen Receptor-T Cell Therapy Patient: A Critical Care Perspective. Society of Critical Care Medicine, 46 (9) 1402-1410.

Karschnia, P. et al. (2019) Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T-cells. Blood First Edition Paper, 893396.

Lee, D.W et al (2018) ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation, 1-14.

Le, R, Q. et al. (2018) FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. The Oncologist, 23 (8), pp. 943-947.

Martinez, M. and Moon, E. K (2019) CAR T Cells for Solid Tumors: New Strategies for Finding, Infiltrating, and Surviving in the Tumor Microenvironment. Front. Immunol., https://doi.org/10.3389/fimmu.2019.00128

Heger (2012): Cancer immunotherapy shows promise in multiple tumor types. http://www.ncbi.nlm.nih.gov/pubmed/22772534

Ramello, M, C. et al. (2018) CAR-T cells and combination therapies: What's next in the immunotherapy revolution? Pharmacological research; 12, p. 194-203

Pang, Y. et al (2018) Advances on chimeric antigen receptor-modified T-cell therapy for oncotherapy https://link.springer.com/article/10.1186/s12943-018-0840-y

Huang, R., Li, X., He, Y. et al. Recent advances in CAR-T cell engineering. J Hematol Oncol 13, 86 (2020). https://doi.org/10.1186/s13045-020-00910-5

Neelapu, S., Tummala, S., Kebriaei, P. et al. Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. Nat Rev Clin Oncol 15, 218 (2018). https://doi.org/10.1038/nrclinonc.2018.20

Santomasso, B. et al (2019) The other side of CAR-T cell therapy: Cytokine release syndrome, neurologic toxicity, and financial burden. American Society of Clinical Oncology Educational Book, 39, 433 – 444

Anderson, K., & Latchford, T. (2019). Associated toxicities: Assessment and management related to CAR T-cell therapy. Clinical Journal of Oncology Nursing, 23(Suppl. 1), 13–19. https://doi.org/10.1188/19.CJON.S1.13-19

https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS27_CART_Facts_2019_FINAL_Rev.1219.pdf

https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/PS100_CART_%202019.pdf

EBMT CAR-T cell e-learning - https://www.ebmt.org/car-t-cell-e-course

Leukemia Care CAR-T e-learning - https://leukaemiaelearning.org.uk/courses/car-t/

www.cancer.gov/about-cancer/treatment/research/car-t-cells

www.learnzone.org.uk

https://learn.nihr.ac.uk/course/view.php?id=411 NIHR e-learning

https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

https://www.bsgct.org/

https://www.esgct.eu/

https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing

https://www.asgct.org/education

Aims and objectives:

Aim

The aim of this workbook is to facilitate the nessesary learning required to competantly manage the care of patients on IEC therapy/trials.

Learning Objectives

- Demonstrate a good knowledge of the theoretical background of IEC therapy for cancer patients including but not limited to:
    - Tumour Infiltrating Lymphocyte (TIL's)
    - Chimeric Antigen Receptor T cells (CAR-T's)
    - T Cell Receptors (TCR's)
- Demonstrate an understanding of the management of a patient undergoing lymphodepleting chemotherapy and the infusion of IECs.
- Demonstrate an understanding of the potential complications of Immune Effector Cell therapy the nursing management of patients receiving IEC therapy
- Demonstrate an understand quality and governance issues in relation to clinical trials and IEC therapy

Introduction to Immune Effector Cells

What is Immune Effector Cell Therapy?

Immune Effector Cell (IEC) therapy is an umbrella term for some types of Advanced Therapy Medicinal Products (ATMPs) which harnesses the bodies immune sytem to fight disease. The term ATMP is widely used in many clinical trials and scientific journals. Adoptive T cell therapy is another term for this process and means using T cells (whether that be the patients own "Auto" or donated T-cells "Allo") to treat the disease. Below is the European Commision definition of ATMPs:

- **Gene therapy medicinal product**

  Contain genes that lead to a therapeutic, prophylactic or diagnostic effect.

  Examples include Chimeric Antigen Receptor T cells (CAR-T) and T Cell Receptor T cells (TCRs)

  Examples include Oncolytic virsus

- **Somatic cell therapy medicinal product**

  Substantially manipulated cells or tissues used to treat, prevent or diagnose disease

  Examples include Tumour Infiltrating Lymphocytes (TILs)

- **Tissue engineered product**

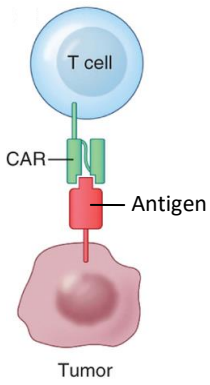
  Cells or tissues that have been modified to repair regenerate or replace human tissue

European Commission – https://ec.europa.eu

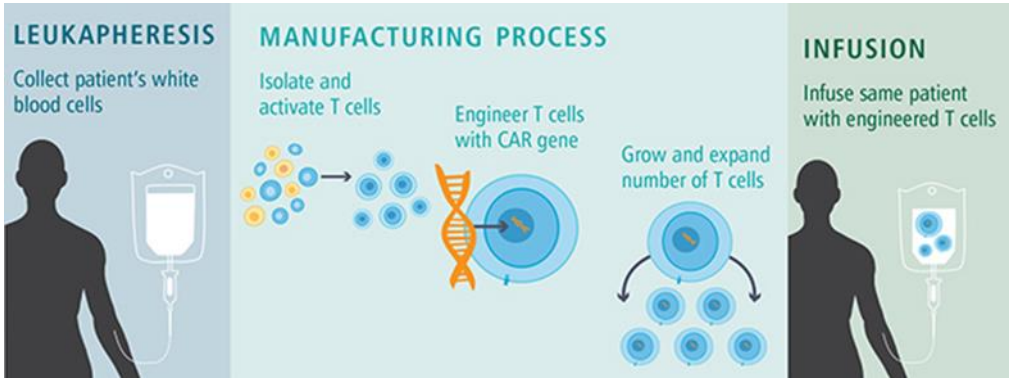
Types of Immune Effector Cell Therapy:

Chimeric Antibody Receptor T Cell (CAR-T): These are T cells which have been genetically engineered to produce a Chimeric Antibody Receptor (CAR) on its surface which will recognise and target specific antigens on the outside of cancer cells e.g. CD19. CD19 is a specific protein marker on the surface of B-Cells and is found on B-cell malignancies such as B cell Lymphomas and Leukaemias. When the CAR regognises and attaches to the target antigen on the tumour cell, the T cell is activated and releases cytotoxic cytokines which kill the cancer cell. The following diagrams represent A) a CAR-T cell and its interaction with a tumour cell B) The process of a patients T cells being taken, engineered and re-infused.

A

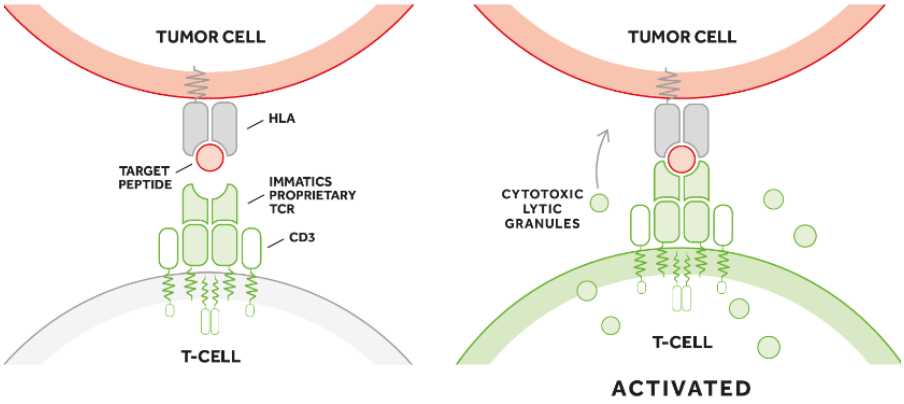


B

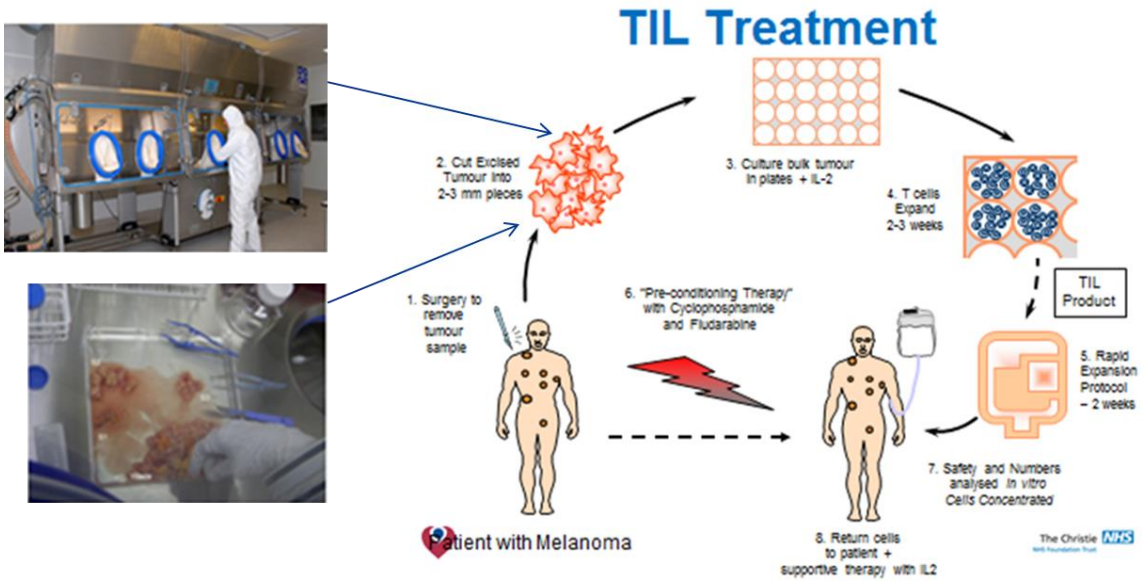


The following video shows how CD 19 CAR-T cells work: https://youtu.be/mXADrg_ckhI

T Cell Receptor T cells (TCR): These are T cells which have been genetically engineered to recognise specific proteins called peptides which are present on the inside of cancer cells but are displayed on the outside of the cancer cell by a protein called a Human Leukacyte Antigen (HLA). HLA is also refered to as a Major Histocompatibility Complex (MHC). An example of a tumour peptide is MAGE-A10 which is present in some Non small cell Lung cancer cells.



Tumour Infiltrating Lymphocyte (TIL): T cells which have managed to penetrate the tumour therefore are isolated, collected and expanded using a special cultures (usually IL2) and then reinfused back into the patient as a form of treatment that is similar to their tumour? . Currently TIL treatment is used for Melanoma patients privately on The Christie clinic however more clinical trials using TILs in other tumours are likely to be seen in the future.



To supplement your learning of this in greater depth and for further information please refer to the following links:

Leukaemia and Lymphoma Society

https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Principles of Chemotherapy and Lymphodepletion

Many clinical trial protocols will use chemotherapy in order to lymphodeplete (remove the patients own lymphocytes) prior to IEC therapy as there is evidence that it can increase tumor specific responses. Lymphodepletion enhances the activity of the transferred IEC by removing regulatory T cells and can activate antigen presenting cells through the induction of inflammatory cytokines and tumor apoptosis.

Administration of preparative regimens: Cyclophosphomide/Fludarabine

Preparation for successful engraftment and expansion of the IECs depends on the specific action of particular cytotoxic drugs given in advance. Clinical trial experience suggests using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy may provide an optimum preparative regime however other lymphodepleting regimes may be used and something to be mindful of.

Cyclophosphamide has been regularly used as a non-myeloablative conditioning regime for IEC therapy which will produce minimal but enough cytopenia to lymphodeplete the patients current T-cells. Cyclophosphamide is in the alkylating agent and nitrogen mustard family of medications. It is believed to work by interfering with the duplication of DNA and the creation of RNA.

Adverse drug reactions from cyclophosphamide are related to the cumulative medication dose and include chemotherapy-induced nausea and vomiting, bone marrow suppression, stomach ache, hemorrhagic cystitis, diarrhea, darkening of the skin/nails, alopecia (hair loss) or thinning of hair, changes in color and texture of the hair and lethargy. Other side effects may include easy bruising/bleeding, joint pain, mouth sores, slow-healing existing wounds, unusual decrease in the amount of urine or unusual tiredness or weakness. Potential side effects also include leukopenia, infection, bladder toxicity, and cancer.

Cyclophosphamide is toxic to the bladder epithelium and when given in high doses can lead to Haemorrhagic Cystitis (HC), associated with microscopic or gross haematuria, to severe haemorrhage with obstructive renal failure. Therefore it is vital to “Ward Test Urine” (Dipstick) each urine sample provided and report result to the medical team urgently. If haemorrhagic cystitis is suspected urine samples should be sent for MSU, cytology, proteinuria and virology. Virology samples should specify the presumed diagnosis of Haemorrhagic cystitis and request PCR testing for Polyoma viruses (BK and JC viruses) and Adenovirus.

A combination of oral/ IV fluid intake of at least 3 litres/day should be maintained during Cyclophosphamide treatment and ideally urine output should be maintained at 100-150ml/hr. With higher doses of Cyclophosphamide, IV Mesna therapy may be prescribed according to the specific protocol. It is important to address the patients symptoms including pain relief analgesia and antispasmodics “buscopan” if required.

For further information please read Q-Pulse Haematology SOP Management of Haemorrhagic cystitis.

Fludarabine is in the purine analog family of medications and works by interfering with the duplication of DNA synthesis by interfering with ribonucleotide reductase and DNA polymerase. It is active against both dividing and resting cells. Fludarabine is associated with profound lymphopenia because of its immunosuppressive effects, and as a consequence, increases the risk of opportunistic infections. Common side effects include nausea, diarrhea, fever, rash, shortness of breath, numbness, vision changes, and feeling tired. Severe side effects include brain dysfunction, low blood cell counts, and lung inflammation. **All patient who have received Fludarabine chemotherapy must have life long irradiated blood products.**

To further supplement your learning here are additional useful links:
https://www.macmillan.org.uk/search/search.html?query=cyclophosphamide&__ncforminfo=U97uX7a6nzu_OE2WdiyCVGvl5ZoykV2zfPcs1zNQolxpf4RV2kmuZ8esbXtuTSmcw5kfTW95QDT8TmqnqT5zEF9egE73Rwyp-CV8qwsjlVI%3D

https://www.macmillan.org.uk/search/search.html?query=fludarabine

Interleukin 2 (IL-2)

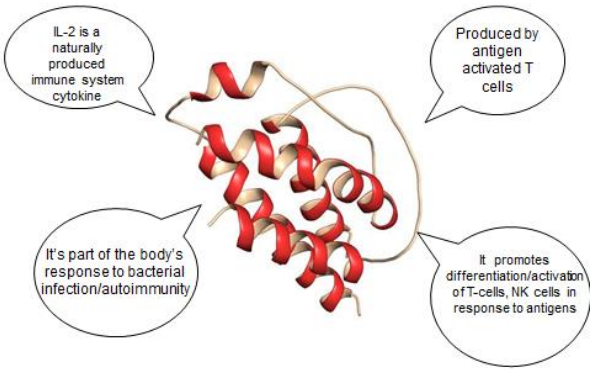
Interleukin-2 (IL2) promotes the survival and proliferation of T cells and has been widely used in experimental cell therapy with TILs - particularly in melanoma. High dose IL2 is used as a stand alone treatment for renal cell carcinoma and is given on Ward 11/12 at The Christie.

The use of IL2 may be indicated at varying doses in some ATMP trial protocols however high dose IL2 is unusual. It is important to understand the rational for use as well as the potential toxicities. Due to the shared clinical profile of the systemic reaction which can occur following IL2 and Cytokine Release Syndrome (CRS) – a common toxicity which can occur following IEC therapy, exposure to patients undergoing high dose IL2 on ward 11/12 is deemed beneficial and will form part of your clinical training programme.

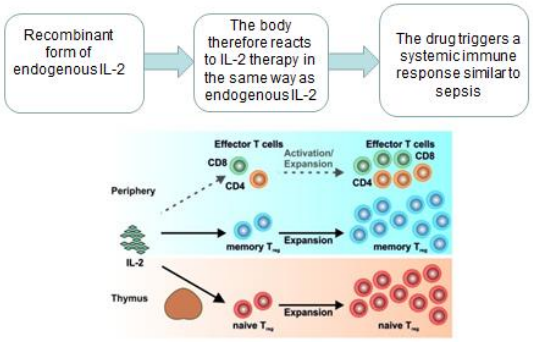
Infusion of high dose IL-2 results in significant systemic toxicity such as capillary leak syndrome (CLS), and an impaired neutrophil function with an increased risk of disseminated infection which may be severe and can result in death. Importantly, these manifestations of IL2 mediated toxicity are shared with other common complications of immune effector cell therapy such as Cytokine-Release Syndrome (CRS), neutropenic sepsis and graft v's host disease, therefore it is vital that the patient is reviewed by the IACT medical team to make a rapid assessment for treatment decisions.

Trust Guidance Policy on HIVE: "Guidelines for the use of High Dose IL2 in Renal Cancer".
The diagrams below describe the function of IL2 as part of the immune system.

Interleukin-2 (IL-2)



Interleukin-2 (IL-2) therapy



Prescribing and Administration of IEC Therapy

Prescribing Immune Effector Cell Therapy

IECs within the context of clinical trials will come under the regulation of ATMPs. Only Principal or sub investigators will have the authority to prescribe ATMPs and in doing so take responsibility that they are competent to do so.

The prescribing of the lymphodepleting chemotherapy regimens and the ATMP will be on iQemo and this prescription must be taken to the patient bedside for safe administration.

Administration of IEC Therapy

On the CRF, the administration of the ATMP will be given by 2 nurses trained in the administration of cells this may be one or two of the AICT Research Nurse and/or the AICT Senior Practice Facilitator. As a ward nurse you will be expected to administer the conditioning chemotherapy and assist in the following interventions specifically for the reinfusion of the ATMP:

- Preparation of the patient includes pre medication and attaching primed giving sets **(this must be a giving set with NO FILTER)** with NaCl 0.9%.
- Preparation of all materials required for infusion/thawing including setting up the water bath and ensuring the **"Emergency Cellular Therapy kit"** is checked and to hand during infusion.
- Recording the patients observation and monitoring throughout the administration process as per the Infusion of Cellular products SOP.
- Completion of related documentation/checklists including Q pulse SOP FRM/SCL/CIFRIP (fresh) or FRM/SCL/THACH (frozen) and ensure this list is returned back to the transfusion main laboratory immediately after the transfusion.
- If the IEC is genetically modified then administration and disposal of waste products must follow the SOP CRF 010.000 - Management of Genetically Modified Waste Generated in the CRF – which can be found on Research Qpulse.
- If an adverse reaction does occur during administration that the medical team are informed immediately, clear documentation of the event is completed and a datix form submitted.

For more detailed training please refer to Q-Pulse Haematology SOP: Infusion of Cellular products.

Due to the shared clinical profile of a stem cell transplant, exposure to clinical experience of these patients on the Palatine ward is deemed beneficial and will form part of your clinical training programme. If cellular therapy activity diminishes on the CRF you will have the opportunity to maintain your competence by revisiting the Palatine Transplant unit - please see the Senior Practice Facilitator to arrange.

Complications and management of IEC Therapy

Cytokine-Release Syndrome (CRS)

A serious side effect associated with IEC therapy is CRS which can potentially have life threatening complication. Early recognition and treatment is key as most patients will make a full recovery. Cytokines are released when T-cells are activated; they are chemical messengers that recruit immune cells. If large amounts of cytokines are released, for instance in a situation where a patient has a large tumour burden for the T cells to react to, the patient can have an overwhelming physiological response which can affect any of the body organs.

Symptoms of CRS often begin with flu like symptoms such as high fevers, aching, chills and fatigue but as the grade of CRS increases symptoms can also include low blood pressure or poor lung oxygenation (requiring administration of supplemental oxygen). Since the signs and symptoms of CRS can mimic sepsis, it is important that patients are treated concurrently for CRS and sepsis. Early escalation of patients to the medical team is vitally important, but initiating sepsis treatment as per Trust policy with broad spectrum antibiotics within 1 hour is the responsibility of the nurse caring for the patient and should be carried out before waiting for a medical review. The onset of these symptoms is typically within the first week of treatment but can be as late as 17 -20 days from initial treatment. CRS is reversible if identified quickly therefore you must be familiar with the CRS grading criteria and CRS management. Early recognition and escalation to the medical team is vitally important.

Patients may require treatment with Tocilizumab which is an IL6 antagonist. Tocilizumab is licenced to treat CRS and is given as an IV infusion of 800mgs over 1 hour. The Tocilizumab will be stored on the CRF if a patient is receiving IEC therapy and if a patient required treatment the Tocilizumab will need to be reconstituted on the ward following standard IV reconstitution guidelines. The patient may receive up to 4 doses of Tocilizumab every 8 hours if required. The decision to treat a patient with Tocilizumab will be made by one of the trial senior medical team.

Nursing staff on the CRF are expected to monitor for CRS and assess this at least twice a day using Appendix A chart on Q-Pulse Haematology SOP: Inpatient management of patients receiving IEC (Including CAR-T cells) and reporting results to medical staff to assess it against the MDACC grading system for CRS.

For further information please read fully the Q-Pulse Haematology SOP: Guidelines for the management of Cytokine-Release Syndrome Associated with Cancer Immunotherapies.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurological toxicity is another potential toxicity following IEC therapy. The pathophysiological mechanism underlying ICANS is still not completely understood. Some potential explanations are the passive diffusion of cytokines into the brain or trafficking of T cells into the CNS.

ICANS can manifests in a variety of ways and include; toxic encephalopathy, confusion, disorientation, agitation, aphasia, somnolence, and tremors. In severe cases of ICANS (grade >2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral oedema can also occur. Often presentation can be subtle with some of the earliest signs being diminished attention, personality change, language disturbance and impaired handwriting. **Most patients who experience ICANS will have reversible symptoms so again early**

recognition and escalation is vitally important. It is also important to note that CRS and ICANS may occur at the same time.

Nursing staff on the CRF caring for an IEC patient will assess patients for Neurotoxicity at least twice a day (more often if clinically indicated) using the American Society for Transplantation and Cellular Therapy, formally ASBMT) consensus criteria recommend assessment according to a 10 point mental state examination (ICE) - see Q-Pulse Haematology SOP: "Neurological Disease in Stem Cell Transplantation and Cellular Therapy Care" for further and additional information.

Principles management for neurotoxicity includes supportive care for grade 1 including Anti-convulsants for seizures, treatment of co-existent CRS if appropriate, steroids for grade 2 or greater, CCU transfer considered for grade 2 and mandated for grade 3-4 disease and Neurology opinion from Salford Royal for all patients.

Note the use of steroids can affect the uptake of T-cells as it suppresses the immune system – something we are trying up build up with ATMP therapy. Therefore steroids must only be administered if prescribed by the consultant after a thorough review and deemed necessary.

Tumour Lysis Syndrome (TLS)

Tumour Lysis Syndrome (TLS) is a group of metabolic complications that can occur due to the breakdown of dying cells—usually at the onset of toxic cancer treatments but can occur up to one month or more after IEC therapy. These metabolites can overwhelm the body's normal homeostatic mechanisms and cause hyperuricemia, hyperkalaemia, hyperphosphatemia, hypocalcaemia and uraemia. TLS can be a life-threatening when leading to acute renal failure but can be managed by standard supportive therapy including IV hydration and IV Raspuricase/ or oral Allopurinol.

Known risk factors include but not exclusive to an elevated LDH (>3xULN), elevated white cell count (>100x109/l or tumour bulk, reduced Glomerular Filtration Rate (<60ml/min) or urinary tract obstruction.

Nursing staff on the CRF are expected to administer prescribed prophylactic IV Raspuricase/ oral Allopurinol and IV hydration when indicated, measure accurate fluid balance and twice daily weight, monitor blood results (Christie Profile and urate) as frequently as required, and administer additional supportive medication where necessary.

For further information please read Q-Pulse Haematology SOP: "Tumour Lysis."

Blood Value Monitoring

Due to the nature of the chemotherapy treatment and medication provided for associated complications in cellular therapy, the patient's full blood count and electrolytes should be monitored closely as per protocol and standard of care- See Routine samples laminate and working instructions per protocol.

Transfusion perspectives/ Administration of blood products

Blood product transfusions may be required in patients who have had IEC therapy. All IEC patients should receive irradiated blood products to reduce the risk of transfusion associated Graft Versus Host Disease for **7 days prior and 6 months post** the IEC infusion. If the patient receives Fludarabine chemotherapy (a purine analogue) **the patient will need lifelong irradiated blood products** as is standard with all purine analogues. You can only administer blood products once you have been fully

trained including the completion of the trusts approved e-learning and administration competency assessment. This will be undertaken by the transfusion practitioner or link nurse, including demonstration of procedures required to complete the CWP Transfusion Care Plan. Where blood product activity diminishes on the unit you will have the opportunity to maintain your competence and carry out this skill in another designated area- please see the Senior Practice Facilitator to arrange.

Please read the Trusts: "Transfusion Policy" for more in-depth information.

Nutritional Support

Patients undergoing IEC therapy may experience varying degrees of malnutrition caused by the cancer or treatment toxicities. Problems such as mucositis, loss of appetite, taste changes and nausea and vomiting can contribute and lead to impaired nutritional status. A Nutritional assessment should be undertaken when patients are admitted for treatment and repeated weekly. Appropriate referral to the dietetic team should be made if intervention is required.

Historic practice was for immunosuppressed patients to follow a 'clean diet' to reduce the potential exposure to pathogens. However, this has limited evidence to support its use and is often difficult for patients to follow. Advice for patients should be to reduce food poisoning risk whilst improving choice at a time when nutritional intake may already be compromised. Strict food-handling and food preparation rules should be followed.

For further information please also read the Trusts policy Nutritional management of immunocompromised patients.

Nausea and Vomiting

Nausea and vomiting is a common side-effect of many cytotoxic drugs and of conditions such as CRS, TLS and sepsis. Nausea and vomiting may cause considerable distress and can also result in serious metabolic disturbances. It is important to administer an antiemetic prior to known emesis causing treatment to avoid this symptom if possible. Cyclophosphamide and Fludarabine are high and severely high emetic risks therefore anti-emetics prophylaxis should be given as prescribed.
For further information please read the Trusts: Clinical Guidance for the Prevention and Management of Chemotherapy and Radiotherapy Induced Nausea and Vomiting in Adults.

Mucositis

Oral Mucositis is defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract. IEC therapy is considered low risk for inducing mucositis as the major cause of it being high-dose chemotherapy- but it is something to be mindful of because it can also be caused by infectious disease, immune deficiency and medications. A baseline assessment (using the WHO Oral Toxicity Scale) of the oral cavity and "pain score" should be carried out on admission and then daily thereafter. This should be documented in your nursing notes as evidence and continuity of care.

For further information please read Q-Pulse Haematology SOP Management of Oral Mucositis in Haematology and Transplant Patients.

Neutropenic fever / Sepsis

Sepsis can be simply defined as a life threatening condition that arises when the body's own response to infection injures its own tissues and organs. An infection is the invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally within the body. Patients who are immunocompromised such as those who have had chemotherapy, which alter the effectiveness of the immune system are more at risk of developing sepsis.
Therefore diagnosing and treating sepsis as quickly as possible is imperative as severe sepsis is a time critical condition. Once being qualified 1 year, National Institute of Clinical Excellence advises for nursing staff to undergo Patient Group Directive (PGD) for first line antibiotics-a written direction relating to administration of a prescription only medicine to a specific group of patients triggering on the 'Sepsis algorithm and is signed in advance by a doctor and pharmacist. As a staff nurse on the CRF, you are expected to participate in this training and the Senior Clinical Practice Facilitator will sign you off as competent to do so, which is repeated every 2 years.

For further information please read the Trust: Guidelines for the management of sepsis (including neutropenic sepsis) or contact the Trust Specialist Sepsis nurse on ext. 8547 for additional support.

Thrombocytopenia, Bleeding and Disseminated Intravascular Coagulation (DIC)

Thrombocytopenia (disease or treatment related) is the most common cause for bleeding in IEC patients as a result of underlying disease or as a result of chemotherapy. The platelet count should be interpreted in the context of the remainder of the full blood count and blood clotting profile. Predisposed causes include: Drug toxicity - many drugs implicated including heparin, antibiotics, quinine and NSAIDs, Chemotherapy, Infection, Nutritional Deficiency, Thrombotic Microangiopathy, DIC, Idiopathic Thrombocytopenia Purpura (ITP) and Liver disease.

DIC is the activation of blood coagulation, generation of fibrin and coagulation of proteins and platelets in organs. The cause is either usually by Sepsis, Trauma, Organ destruction e.g. pancreatitis, Solid tumours, Leukaemia, Vascular aneurysm, Severe liver failure, ABO transfusion incompatibility or Transplant rejection. Symptoms of DIC include Thrombosis, Embolism, Organ dysfunction or Active bleeding. Management of DIC is to treat the underlying disorder and then supportive treatments include Platelets and FFP, Cryoprecipitate and Anti-coagulants.

For further information please also read Q-Pulse Haematology SOP Thrombocytopenia, bleeding and DIC.

Haemophagocytic lymphohistocytosis (HLH) and Macrophage Activation Syndrome (MAS)

HLH and MAS describe a rare spectrum of disorders resulting from uncontrolled activation of T-lymphocytes and macrophages.

HLH/MAS can be challenging to diagnose but some of the characteristic features are Fever, Splenomegaly, Pancytopenia (Hb <90g/l, platelets <100x109/l, neutrophils <1x109/l), Lymphadenopathy, Hepato-splenomegaly, Neurological symptoms (not specific including ataxia, confusion, seizures), Rash. Patients with suspected HLH and grade ≥3 organ dysfunction should be

treated with CRS protocol with treatment aimed at the underlying cause (if known and reversible) and controlling the uncontrolled immune response initially of steroids, etoposide and cyclosporine.

For further information please also read Q-Pulse Haematology SOP HLH and Macrophage activation syndrome.

Renal Disease inc. Thrombotic Microangiopathy (TMA) in Cellular Therapy

Renal disease may be seen as a common complication of cellular therapy and precipitating factors include prior renal disease, cytokine-mediated vasodilation, decreased cardiac output as a consequence of sepsis or CRS, intravascular dehydration due to insensible losses from high fevers, Tumour lysis syndrome or Drug toxicity (inc. antibiotics, calcineurin inhibitors, antihypertensive, NSAID).

AKI alerts are automatically generated with patient blood results on the Clinical Web Portal. This is a staging 1-3 measure of changes to the renal function and should such incidence occur please report to the medical team and the Trusts AKI specialist nurses on ext. 8547 for additional support.

TMA is a rare but significant complication of cellular therapy and the mortality is very high. Symptoms include neurological headaches, confusion, change in personality (including irritability), seizures, pyrexia, thrombocytopenia and haemolysis or microangiopathy. The only proven beneficial management for these patients is cessation of the calcineurin inhibitor drugs, and more recent data has reported the efficacy of eculizumab drug too.

Patients with renal disease require comprehensive nursing and medical care. For further information please read Q-Pulse Haematology SOP: Renal disease following stem cell transplantation and cellular therapy including Thrombotic Microangiopathy (TMA) and the Trusts policy: Clinical Guidance for Acute Kidney Injury.

Respiratory Disease/Distress in Cellular Therapy

Respiratory disease can be common toxicities associated with IEC therapy particularly in the context of CRS. Infection is a significant cause of respiratory associated morbidity following cellular therapy and chemotherapy despite antibiotic prophylaxis prescribed. Treatment for the following respiratory infections include: Influenza A/B Oseltamivir or Zanamivir orally; or for Respiratory Syncytial Virus (RSV); Parainfluenza and Metapneumovirus viruses are treated with Nebulised Ribavirin.

IEC allogeneic patients are also at risk of CMV pneumonitis although the risk of infection (rather than asymptomatic viral reactivation) is reduced by monitoring bloods and pre-emptive treatment. For further information please read Q-Pulse Haematology SOP: Prevention, diagnosis and management of CMV disease (cytomegalovirus) In Stem Cell Transplant Patients.

For additional information please read Q-Pulse Haematology SOPs: Respiratory Disease following stem cell transplantation and cellular therapy; Treatment of Respiratory Viruses with Ribavirin and Pandemic Influenza.

Cardiovascular disease/ dysfunction in cellular therapy

Cardiac disease and cardiovascular toxicity can be a toxicity associated with stem cell transplantation. Patients will be assessed before cellular therapies for evidence of cardiac disease which may lead to an increased incidence of post-transplant cardiac complications with an ECG/ECHO.

Cardiac dysfunction particularly in the context of CRS associated with IEC therapy may present as tachycardia especially with fever, capillary leak, arrhythmias, hypotension, elevated troponin, cardiac failure with risk of sudden cardiac death. Blood pressure must be regularly monitored and persistent blood pressure above 140/90 mmHg or isolated above 180/100 should be escalated to the medical team immediately.

Patients with evidence of cardiovascular disease should receive supportive care according to the Trusts: National Early Warning Score 2 (NEWS2) and observation policy for the management of acutely ill adult patients and Outreach and CCU support should be requested as indicated by the patient's clinical condition.

For further information please read Q-Pulse Haematology SOP Cardiovascular disease following stem cell transplantation and cellular therapy.

Hepatic failure

Sinusoidal obstruction syndrome (SOS) is now the preferred reference over Veno-Occlusive Disease (VOD), is a potentially serious complication of high dose chemotherapy and IEC therapy. The clinical symptoms of SOS include weight gain, increased abdominal circumference, hepatomegaly, right upper quadrant pain, ascites and elevated total and direct bilirubin. The drug treatment for this condition is IV Defibrotide QDS and then high levels of nursing and medical monitoring. For further information please read Q-Pulse Haematology SOPs: Hepatic Veno -occlusive Disease (Sinusoidal obstruction syndrome) and Liver dysfunction.

Viral infections are a significant cause of post-transplant hepatitis. The most common causes of serious disease are EBV, Adenovirus, HSV, VZV and hepatitis B. HSV and VZV can be largely prevented with prophylactic acyclovir. IEC autologous transplants are considered low risk and therefore CMV and EBV monitoring are only required if symptomatic- this would be 7.5mls venous blood obtained in an EDTA bottle and sent for PCR.

Please also read Q-Pulse Haematology SOPs: Virology- Allogeneic and Autologous Hematopoietic stem cell transplant patients.

Additionally a useful learning tool to aid your learning has been released by European Bone Marrow Transplant Committee and is on the following link:

https://www.ebmt.org/veno-occlusive-disease-vod-learning-programme

Supportive medications- Prophylaxis and antifungals, inc. pain relief and anti-emetics

Depending on the patient's prior disease and treatment history, patients having cellular therapy products may be at increased risk of infection, particularly during periods of neutropenia or

prolonged immunosuppression. Autologous cellular therapy patients are generally considered to be low risk however an appropriate prophylactic regime should be prescribed for all patients tailored to their level of risk and knowledge of previous infections. Attention should also be paid to preventing exposure to fungal pathogens through cleaning procedures and good hygiene.

Individual protocols may state the particular prophylaxis required; others may ask to use the trusts 'standard of care'. Standard of care prophylaxis medication for IEC patients include:

- Antibiotics- Levofloxacin 500mg OD
- Antivirals- Aciclovir 400mg BD
- Antifungals- Posaconazole 300mg OD or Fluconazole 200mg OD
- Pneumocystis Jirovecil cover- Co-trimoxazole 960mg Mon, Wed, Fri
- Allopurinol 300mg OD (Only if required for TLS prophylaxis)
- Noristerone 5mg OD-TDS. (For females of child bearing potential)
- Dalteparin - LMWH 5000u SC OD unless platelets <75
- Lansoprazole 30mg OD

Common supportive antibiotic treatments include:

1st line is Tazocin for gram positive bacteria and usually given with Gentamicin for Sepsis but can be given as monotherapy for chest sepsis.

Gentamicin treats gram negative aminoglycosides. It is contraindicated with platinum based chemotherapies within 7 days and the patients should have daily serum creatinine. Gentamycin should be avoided if renal function is worsening and to note a blood level is required before the 2nd does is given- to be <1.

Meropenum Carbapenems treats both gram positive and gram neg bacteria and is an alternative to Taz and Gent for first line antibiotics.

Vancomycin Glycopeptide treats gram positive bacteria for line infection, mucositis, or orally for C-Difficile. Note a blood level is required before the 3rd dose and results reviewed before the 4th dose is given (level >15 omit/dose reduce).

For further information please also read Q-Pulse Haematology SOPs Haematology Summary of Prophylaxis and Antifungal prophylaxis and treatment.

Daily Nursing Management

Specific daily nursing management responsibilities are required for IEC patients because their unique clinical needs.

Fluid monitoring: allows to carefully monitor the fluid input and output through calculation of fluid balance. Please use the Trusts A3 fluid balance charts and for IEC patients monitor at a minimum of 4 hours or more regularly if required. If there are any queries of accuracy, ensure twice daily weights and report to medical staff.

Monitoring and recording of observations: This should be conducted via NEWs2 charts and include temperature, pulse, blood pressure, oxygen saturations and respirations in alignment with Haematology Qpulse SOP: Nursing Observations for all Haematology and Cellular therapy patients and The Trusts: National Early Warning Score 2 (NEWS2) and observation policy for the management of acutely ill adult patients guidance as well as any trial specific work instruction.

There are also several daily nursing checks required to ensure the patient is being monitored in all areas. These must be fully documented in the patients CWP nursing care plans for patient continuity. Please refer to the 'Daily Check Chart'.

PGDs for Anaphylaxis cover on the CRF. The Resuscitation Council UK guidelines cover Registered nurses for the administration of IV fluid bolus saline challenge (2 x 250mls STAT), Chlorphenamine 10mg, Hydrocortisone 200mg and IM Adrenaline 1 in 1000 (500mcg) as part of their anaphylaxis algorithm. However it is also possible to administer these drugs under a PGD and this will be conducted by the Senior Practice Facilitator for cellular therapy or ward sister to assist your rapid response if complications resulting from cellular therapy care arise for the benefit of patient care.

For further guidance please read the following Q-Pulse Haematology SOPs:

- Inpatient Management of Patients receiving immune effector cells (including CAR-T cells)
- Infection Prevention and Control procedures in the clinical facilities
- Fluid balance (Recording and monitoring)
- Nursing Observations for all Haematology and Cellular therapy patients
- Trust: National Early Warning Score 2 (NEWS2) and observation policy for the management of acutely ill adult patients

Teenage and Young Adults

Adolescence is the period of psychological, social and physical transition between childhood and adulthood. The World Health Organisation (WHO 2015) defines adolescence as:

"…..the period of life between 10-19 years, youth as between 15-24 years and young people, as those between 10-24 years" .

Working with young people requires a detailed understanding of their development and behaviour, in order to support them in the most appropriate way.

For further information please also read Q-Pulse Haematology SOP: TYA Training Workbook.

Key TYA Personnel

- Anna Mackland, Occupational Therapist ext 3399 or bleep 12048
- Nicola Chesman, Physiotherapist ext 3399 or bleep 12047

- Hanna Simpson, Clinical Liaison Nurse Specialist 07920 701747
- Charlene Jones, Teenage Cancer Trust Clinical Liaison Nurse Specialist 0777 6162791
- Martha Jones, Clinical Liaison Nurse Specilalist, Teenage and Young Adults 07721879437
- Kate Law, Clinical Nurse Specialist 0161 446 3955 Mobile; 07721 879 437
- Stephen Harcourt, Youth Support Coordinator ext 7034
- Lorraine Wright, Support & Activity Co-ordinator ext 8085
- Clic Sargent Social Workers Esther/ Eilis 8094

TYA Suggested Reading

World Health Organisation (2015) Adolescent Health
http://www.who.int/topics/adolescent_health/en/

Cancer Research UK Teenage and Young Adult Cancer (2015)
http://publications.cancerresearchuk.org/publicationformat/formatstats/tya- report.html

A Blueprint of Care for Teenagers and Young Adults with Cancer (2012)
https://www.teenagecancertrust.org/sites/default/files/Blueprint-of-Care.pdf

Children's Oncology Group (2010) Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers (version 3). Available from www.survivorshipguidelines.org

Governance

ATMPs/IECs are unique in that when the initial cells or tissue is taken from the patients the tissue/cells comes under the regulation of the Human Tissue Authority (HTA), however once the tissue/cells have been manipulated or engineered they are considered to be a medicinal product (ATMP) and are regulated as any other medicinal products by the Medicines and Healthcare products Regulatory Agency (MHRA). All ATMPs have strict regulations in terms of their traceability. This means there are strict processes to follow at every stage of the patient pathway from tissue/cells leaving the patient, through any processing until the ATMP is returned to the patient. Close collaboration between the tissue or stem cell labs and Pharmacy are required to ensure regulations and legal requirements are adhered to.

Human Tissue Authority

The Human Tissue Act 2004 covers England, Wales and Northern Ireland. It established the HTA to regulate activities concerning the removal, storage, use and disposal of human tissue. When IECs are initially procured (cells from apheresis and solid tumour collections for TILs) they are still considered Human Tissue and are regulated by the Human Tissue Authority. You will be provided with role appropriate HTA training.

For further reading please access the link below:

https://www.hta.gov.uk/policies/human-tissue-act-2004

Medicines and Healthcare products Regulatory Agency (MHRA)

Once cells have been manipulated (Genetically modified or cultured and expanded in the lab, they are then considered to be a medicinal product and from that point are regulated by the MHRA.

Principles of JACIE/FACT

Applied to the Christie R&D Quality Management System and the CRFs Education Programme.

The **J**oint **A**ccreditation **C**ommittee of **I**SCT (International Standards for Cell Therapy) & **E**BMT (European group for Blood and Marrow Transplant) – JACIE, was established for the purpose of assessment and accreditation in the field of haematopoietic stem cell transplantation (HST) and more recently incorporates standards for the administration of IECs. All clinical facilities with JACIE accreditation who deliver IECs as well as HST must adhere to these additional standards. Therefore training outlined in this workbook adheres to these standards set out by JACIE in alignment with the Palatine ward and The Christie Private Care HTU ward.

Training on the CRF aims to follow JACIE guidance in the context of theory based and practical education- in the form of specialist workbooks, competency objectives, placements, in-house basic and advance study days and direction to additional e-learning.

For further information please also read Q-Pulse Haematology SOP: Nurse & AHP training and Education.

Immune Effector Cell Practice Placements

Name: Date:

The list of objectives below are to provide guidance on the key areas for observation during the clinical placements. Any objective not met on placements will be covered in discussion with the Senior Practice Facilitator on return to the CRF.

Learning Objective	Objective Specifics	Date	Signature of Learner/ Mentor
Nursing Handover	Observe the content, accuracy and flow of a routine handover AM/PM shift for cell therapy patients.		
Medication Training/ Routine drugs round	Observe and participate in at least x 2 drugs rounds to familiarise self with drugs commonly used in transplant/cellular therapy care taking note of: • Anti-fungal • Anti-viral • Antibacterial Aware of the term prophylaxis and where appropriately prescribed/ administered on drugs Kardex. Aware of how to access Medusa for common drugs. Demonstrates an awareness of antibiotic levels and when to take for Gentamycin and Vancomycin		
Routine Observations/ Vital signs monitoring	Conduct routine observations on cell therapy patients and document appropriately. Observe usage of NEWs2 on CWP care plan.		
Sepsis	Observe the process of applying the Trusts Sepsis algorithm- the "3in/3out" requirements inc. PGD antibiotics and PGD Saline Bolus. Observe the process of reporting sepsis review to medical and outreach services and the commencing of the Infection CWP care plan. Undertake PGD training with Senior Practice Facilitator before participating in the assistance of first line IV Antibiotics and Saline PGDs.		
Routine Daily Checks inc. Oral hygiene and body weigh	Observe and assist in undertaking and documentation for a transplant patient: Line inspection, Visual body checks (Rashes/ pressure care), Oral hygiene, Bowel motion monitoring. Awareness of weighing IEC patients daily/ twice		

	daily. Observe and assist in the assessment of the patient's routine mouth condition using the WHO Oral Toxicity Scale. Clearly document any changes in the oral mouth and communicate this with the senior nursing and medical team. Observe and assist in being able to advise the patient on the correct oral hygiene methods including an awareness of the mouth care products available.		
Fluid balance and urine testing	Aware of the accurate measurement of bodily fluids with weighing scales. Aware of the importance of an accurate documentation on the trusts new fluid balance charts. Aware of the signs and symptoms if a patient is in fluid overload or dehydrated and reporting to medical team if the patient is in a negative or positive fluid balance. Awareness for routine "Ward Test Urine" urinalysis "dipstick" for infection/ haemorrhaging cystitis/ diabetes etc. and reporting any abnormal results to the medical staff.		
Specimen collection	Aware of the equipment required to obtain specimens of: • Urine – MSSU/ CSSU • Faeces • Sputum • MRSA swabs • Wound swabs • Nose and Throat swabs Aware of the process for specimen collection required: • On admission • Weekly • If Septic • If patient symptomatic i.e. diarrhoea/ dysuria/ respiratory symptoms Awareness of where to accurately record sample collection.		
Nutrition	Aware of the need for assessment of patient's dietary intake and implements the commencement of food charts when required. Recognises when to refer patient to a dietician and how to refer. Aware of the dietary alternatives/supplements available to the patients as prescribed such as		

	fortisips.		
Blood results monitoring	Be familiar with any blood test relevant to a particular type of treatment/protocol. Assist in acting on any prescribed replacements for the transplant patient including electrolyte or blood product replacements.		
Transfusion Administration of blood products	Once re-completing the trusts e-learning and theory practical and signed off as competent you must: Observe the CWP process of the electronic prescription and care plan for blood products including the ordering, ready for collection, pre transfusion observations and line set up, teletracking process for delivery, product receiving, administration process, 15 minute observation recording and end of transfusion process. Then administer under direct supervision: x2 Blood transfusion products x2 Platelet transfusion products To repeat this process every 4 month if not a skill frequently practiced and confident in.		
Medical Devices	Observe and assist in the safe administration of several IV infusions being administered at any one time for a cell therapy patient using a Baxter/graesby pump. Awareness of the infusion pumps being cleared at 6am each day and the "total volume infused" is recorded at a minimum of every 4 hours on the patients fluid balance chart (or more often as required).		
SACT administration in IEC work up regimens	Observe a patient receiving a lymphodelpeting work up regime (e.g.Cyclo/fludarabine) Awareness of the side effects of each drug involved. Awareness of requirements for Mesna and IV fluids for high dose cyclophosphamide. Awareness of appropriate antiemetic cover for each drug involved. Awareness of the extravasation policy and chemotherapy spillage kit.		
Practical Training for Infusion of Frozen Stem Cells/ Cell therapy	Observe the process for x1 frozen cells for: Setting up (pre meds/lines/emergency kit check/ flushes/documentation required/ water bath set up).		

	The process of supporting an infusion – Paperwork requirements for administration timings- start/stop times and observation documentation. Post infusion (observations/ documentation signing, equipment cleaning).		
Practical Training for Infusion of Fresh Stem Cells/ Cell therapy	Observe the process for x1 fresh cells for: Setting up (pre meds/lines/emergency kit check/ flushes/documentation required/ water bath set up). The process of supporting an infusion – Paperwork requirements for administration timings- start/stop times and observation documentation. Post infusion (observations/ documentation signing, equipment cleaning).		
Grading of IEC Specific Toxicities	Observe accurate grading of CRS as per the CRS SOP – discuss management of patient with all grades of CRS. Observe accurate grading of Neurotoxicity using the American Society for Transplantation and Cellular Therapy ICE Score criteria as per the Neurotoxicity SOP – discuss management of patients with all grades.		
Controlled Drugs	Observe and participate in the awareness for usage, frequency and familiarity of commonly used controlled drugs for transplant patients include appropriate doses, routes, duration etc.		
Infection control	Awareness of the impact infection can have on an immunocompromised patient. Aware of the methods of isolation and the correct use of appropriate protective equipment. Aware of the importance of daily cleaning of patient's rooms and the correct procedure. Aware of the procedures followed to clean a room when a patient has been discharged. Observe and participate in the correct procedure when dealing with: • Bed linen from infected patients • Disposing of contaminated bedpans/ bottles/vomit bowls		
Multi- Disciplinary Teams	Awareness of the following team members roles and how to refer to the patients: Medical Team Research Team Outreach / Critical care Team Pharmacy Community Link Team / District Nurse Team		

	Dietician Occupational Therapist Physiotherapist Complimentary Therapist Psycho Oncology Team Supportive Care Team Social Workers Chaplain PALS- Patient Advice and Liaison Service		
Tele-Tracking	Observe and participate in the practical use of Tele tracking when necessary to order/request services e.g. blood products, portable oxygen, specimen collection etc.		
Q Pulse	Observe and become familiar with the usage of Qpulse software and situations when SOP guidance is referred to on this system.		
Observation of management of IL2 patient	Observe the process for a IL2 patient for: Setting up (pre meds/lines/check/ flushes/documentation required). The drawing up and administration process of IL2 Post infusion (observations/ documentation/ IV hydration algorithm). Awareness of IL2 policy and when to report patient's observations and clinical picture to medical team. Discussion of management of adverse reactions during IL2 treatment.		
Observation of management of TILs patient	Observe the process for a TILs patient for: Setting up (pre meds/lines/ flushes/documentation required). The administration process of TILs Post infusion (observations/ documentation/ IV hydration algorithm). Awareness of TILs SOP and when to report patient's observations and clinical picture to medical team. Discussion of management of adverse reactions during TILs treatment.		

APPENDIX A: IEC/Cellular Therapy SOPs and Trust Guidelines

Topic	Haematology SOP/ Trust Policy	Code	Version and Date	Name	Signature	Role	Date
Management of immune effector cells	Inpatient management of patients receiving immune effector cells (Including CAR-T cells).						
Cytokine-Release Syndrome	Guidelines for the management of Cytokine Release Syndrome Associated with Cancer Immunotherapies						
Immune Effector Cell-Associated Neurotoxicity Syndrome	Neurological Disease in Stem Cell Transplantation and Cellular Therapy Care						
Neutropenic fever / Sepsis	Trust: Guidelines for the management of sepsis (including neutropenic sepsis)						
Tumour Lysis Syndrome	Tumour Lysis						
Blood value monitoring inc. Electrolyte imbalances and IV hydration	Trust: Clinical guidance for IV fluid prescribing in adults Trust: Medicines Practice Operational Policy						
Transfusion perspectives/ Administration of blood products	Trust: Transfusion Policy						
Nutritional Support	Nutritional management of immunocompromised patients						
Nausea & Vomiting	Trust: Clinical Guidance for the Prevention and Management of Chemotherapy and Radiotherapy Induced Nausea and Vomiting in Adults						
Mucositis	Management of Oral Mucositis in Haematology and Transplant Patients						
Thrombocytopenia, bleeding and DIC	Thrombocytopenia, bleeding and DIC						
HLH and Macrophage activation syndrome	HLH and Macrophage activation syndrome						
Renal disease inc. TMA in cellular	Renal disease following stem cell transplantation and						

therapy	cellular therapy including Thrombotic Microangiopathy (TMA)						
Respiratory disease/distress in cellular therapy	Respiratory Disease following stem cell transplantation and cellular therapy						
Cardiovascular disease/ dysfunction in cellular therapy	Cardiovascular disease following stem cell transplantation and cellular therapy						
Haemorrhagic Cystitis	Management of Haemorrhagic cystitis						
Hepatic failure inc. VOD	Hepatic Veno-occlusive Disease (Sinusoidal obstruction syndrome) and Liver dysfunction						
Supportive medications-Prophylaxis	Haematology Summary of Prophylaxis Antifungal prophylaxis and treatment						
Daily Nursing Management	Fluid balance (Recording and monitoring) Nursing Observations for all Haematology and Cellular therapy patients Trust: National Early Warning Score 2 (NEWS2) and observation policy for the management of acutely ill adult patients Nurse & AHP training and Education Infection Prevention and Control procedures in the clinical facilities						
AKI	Trust: Clinical Guidance for Acute Kidney Injury						
Influenza	Pandemic Influenza Treatment of Respiratory Viruses with Ribavirin						
CMV	Prevention, diagnosis and management of CMV disease (cytomegalovirus) In Stem Cell Transplant Patients.						

Virology	Virology- Allogeneic and Autologous Hematopoietic stem cell transplant patients						
Extravasation	Management of Extravasation Policy						
GVHD	Graft Versus Host Disease (GvHD) prophylaxis Diagnosis and Management of Acute and Chronic Graft Versus Host Disease (GvHD)						
Administration of cells	INFUSION OF CELLULAR PRODUCTS						
CVAD	Central Venous Access Device Policy (CVAD)						
TYA Training Workbook	Palatine Ward TYA Training Workbook						