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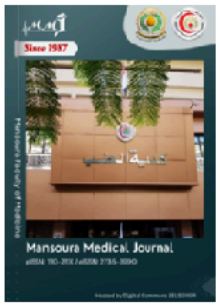

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Could CAR-T cell therapy be a promising agent in acute lymphoblastic leukemia?

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- Pain
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Abstract

Postoperative anal pain is one of the main adverse effects of surgical treatment of benign anorectal diseases and remains a distressing problem, for both patients and physicians. Postoperative pain control is important yet it remains an unresolved issue which causes patient dissatisfaction and negatively impact quality of life. This review article studied the analgesic effect of topical and oral metronidazole after benign anorectal surgery. Seven studies used oral metronidazole and six used topical metronidazole. The studies showed that post operative pain score of patients who had metronidazole by either route was significantly less than those in comparison groups. The pain score decreased at all the time points for both oral and topical metronidazole. Overall, the analgesic effect of oral metronidazole was inconsistent among published studies. When topical and oral metronidazole were compared the post operative pain score and analgesic consumption were lower in topical metronidazole than the oral group

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INTRODUCTION

Immunotherapy is now a pillar of cancer therapy. In which, it mediates its effect through activation of the host immune system to fight malignant cells, different from chemotherapy, which exert its effect by cytotoxic properties.

Many immunotherapies have been developed such as vaccines and antibody therapies. We are going to focus on Chimeric Antigen Receptor (CAR) T-cell

therapy and it is role in acute lymphoblastic leukemia treatment (1).

CAR T-cell therapy is a recent modality which uses the own T cells of the patient, CAR which represents the genetically engineered and modified fraction of the T cells, includes protein that permit T cells to attack the malignant cells. CAR T can provide long term control of the disease and potential protection against relapse (2).

T-cell activation

Signal one

(Antigen Processing & Presentation)

T cells are developed in the thymus gland to be specific for antigen. $CD4^+$ helper T-cells and $CD8^+$ cytotoxic T-cells recognize their antigen which is attached to major histocompatibility complex (MHC), found on APC's surface. This triggers and aids the initial activation of the T cells(3).

Signal two

(Co-stimulation)

After T cell receptor (TCR) binds to antigen-loaded MHC, both $CD4^+$ and $CD8^+$ T cells will be activated by 2ry signals and respond potently to the pathogen. For $CD4^+$ T cells, **CD28** will provide the 1^{st} signal. (3). While, $CD8^+$ T cells activation needs signals from 4-IBB(CD137) and CD 70 (3)**Fig 1**.

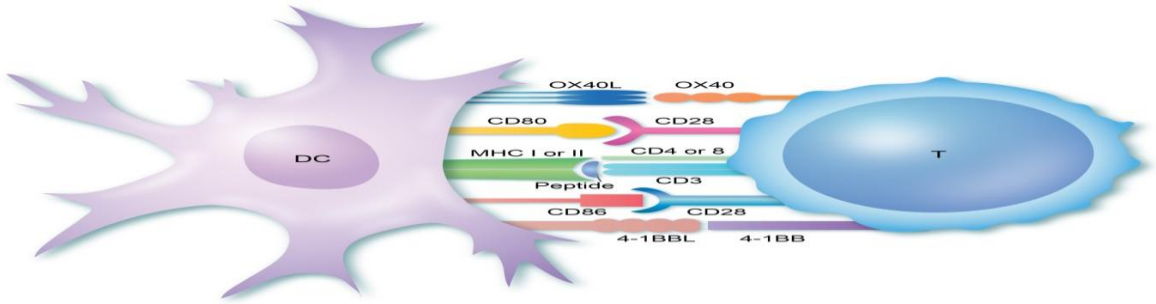

Figure 1. Schematic of early T cell activation **(3).**

Signal three

After the second signal, T cells subtype will be identified based on specific antigen signal and cytokines (3).

Chimeric antigen receptor design

CAR T cells are manufactured by introducing a genetically engineered CAR fusion protein by means of a retrovirus into autologous T-cells. Recently approved CAR T-cells use CAR constructs consisting of a single‐chain variable fragment antigen‐recognition domain, a

CD3‐derived T‐cell activation domain and a co-stimulatory domain (CD28 and/or 4‐1BB) (4). **Fig 2**.

First-generation CARs failed to make antitumor effects. It consists of a CD3 domain and a tumor antigen-binding domain (5).

Second-generation CARs provide a better cytokine production and proliferation

Third-generation CARs have a better effect than 2nd generation due to two co-stimulatory domains (CD28 or CD137 and/or others as ICOS, CD27, or CD134) addition (5).

The fourth generation CAR is engineered with a cytokine (IL-12). The T cells are directed for antigen-unrestricted cytokine-initiated killing (known as TRUCK T cell) have the ability to liberate

this transgenic protein to regulate T-cell response. The advantage of 4th generation CAR -T is the ability to also reactivate innate immune cells to attack the antigen

-negative cells & self-withdrawal mechanism, once antitumor effect is achieved (5).because of co-stimulatory domain (CD28 or CD137) addition (5).

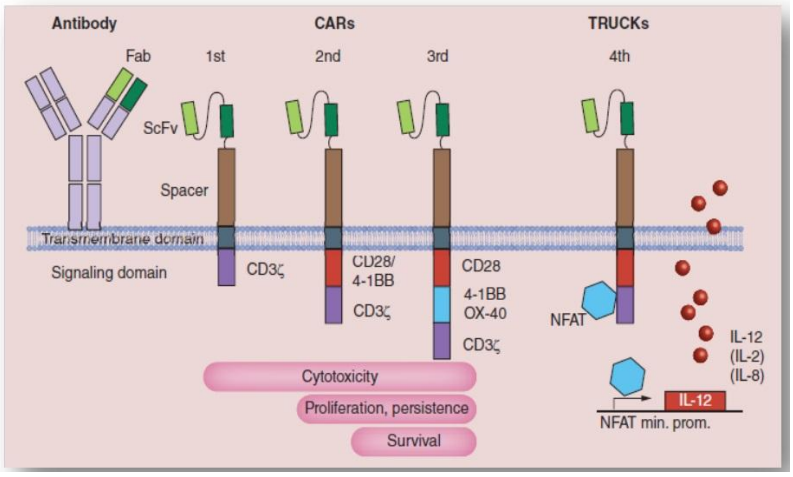

Figure 2. Schematic representation of four types of CARs (6)

Chimeric Antigen Receptor mechanism

Choosing an ideal target is essential in the design of powerful cellular immunotherapies and to minimize the toxicities. CD19 antigen remains the most widely used as it is upregulated on malignant B cell (7, 8) **Fig 3**.

Tisagenlecleucel activation is achieved through 4-1BB (CD137), which is essential to activate nuclear factor-kB (NF-kB) via p38 mitogen-activated protein kinase (MAPK) and Jun N-terminal kinase (JNK)(9).

Downstream to this activation of NF-kB, phosphoinositide 3 kinase (PI3K) and protein kinase B (PKB), 4-IBB then upregulates anti-apoptotic factors such as Bcl-2, Bcl-xl, and Bfl-1(9).

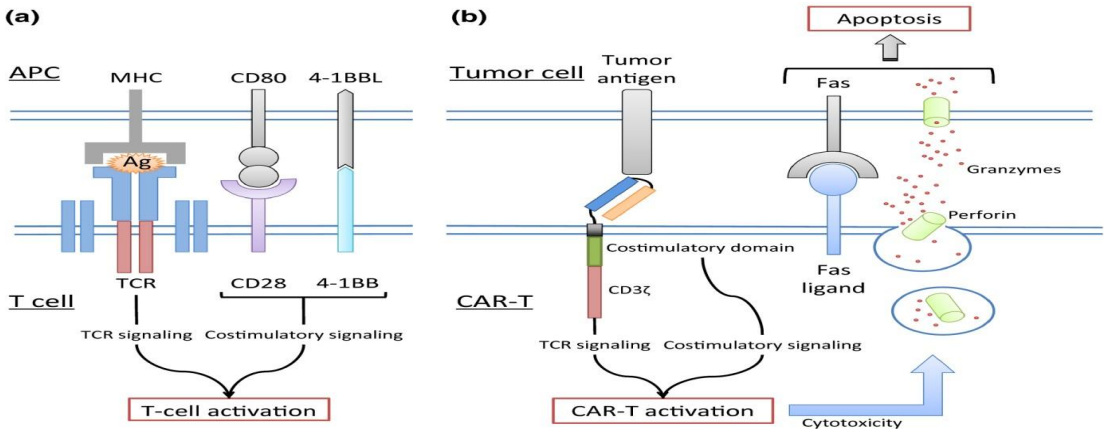

Figure 3. Anatomy for T cell engineers: T cell receptor and CAR binds to surface molecules on tumor cells (10)

It also acts through interaction with endogenous TCR signaling leading to T-cell proliferation, cytokine secretion, cell-cycle progression via extracellular signal-regulated kinase (ERK) and PI3K, prevention of clonal deletion(11).

CAR T-Cell therapy phases

Initially patient's evaluation for CAR T-cell therapy eligibility will take place, followed by the leukapheresis. After that, the collected T cells are transferred for manufacturing in the laboratory. During this time, the patient will receive lymphodepleting conditioning chemotherapy that will aid preparing the immune system to support this therapy, Table 1(12).

Table 1.Six Phases Of CAR T-Cell Therapy(12)

Phase	Definition	Key features	Patient education considerations
Consultation and workup	Evaluation of patients for CAR T cell therapy eligibility.	This includes confirmation of patient eligibility to ensure readiness for therapy.	It includes structured history, physical examination, and laboratory investigations.
Leukapheresis	It consists of WBCs collection from the patient through apheresis catheter.	Laboratory criteria, such as complete blood count, is considered.	Education for patient & caregiver should focus on the leukapheresis procedure and side effects, such as fatigue, cytopenias, or hypocalcemia.
Bridging	After WBCs collection from the patient, the T cells are separated and sent to the manufacturing facility where they undergo genetic modification to express the specific CAR.	Manufacturing sometimes may be unsuccessful because of the product being out of FDA specification. Options may include a second leukapheresis.	Manufacturing takes at least 2 weeks. Chemothrerapy is used during this phase to prevent relapse, debulk the tumor, and maintain performance status without undue toxicity.
Lymphodepleting chemotherapy	This phase includes re-staging the patient and the delivery of lymphodepleting conditioning regimen before CAR T-cell infusion.	Regimen includes fludarabine and Cyclophosphamide given over 3 days.	Conditioning regimen may be received in the inpatient or outpatient setting.
Infusion and monitoring	This phase includes CAR T cells infusion and observation during and post- infusion for toxicities and response.	The specifics on infusion of CAR T-cell products are well defined in package inserts per FDA guidelines.	When the CAR T cells begin attacking cancer cells, they proliferate and can cause manifestations of CRS and neurologic toxicity.
Long-term follow-up	This phase includes re-staging, which is done 30–90 days post-infusion.	Follow-up may include peripheral flow cytometry, BMA and biopsy.	Following treatment, patients' needs accurate follow-up to manage complications .

CHIMERIC ANTIGEN RECEPTOR CELLS TOXICITY

While CAR T-cell therapy has shown impressive results, acute toxicities can be fatal such as cytokine release syndrome (CRS) and neurological toxicity, immune effector cell-associated neurotoxicity syndrome (ICANS). Also delayed toxicities as B-cell aplasia, prolonged cytopenias and risk for opportunistic infections are being clearly recognized (13)**fig.4.**

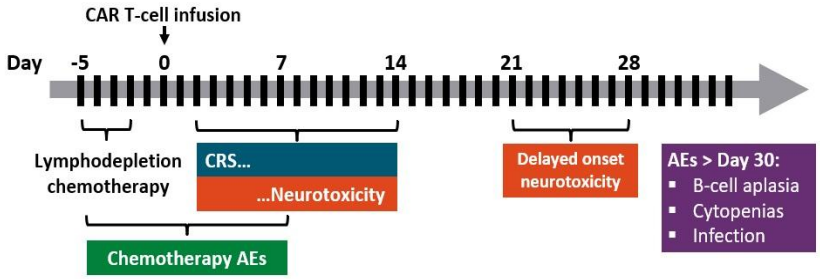

Figure 4.CAR T-Cell Toxicities Timeline (14).

CRS is an inflammatory syndrome caused by numerous cytokines and inflammatory markers such as C-reactive protein, ferritin, interferon-ϒ, interleukins, and macrophage inflammatory protein-1(13).

ICANS can occur alongside with CRS or more after CRS been settled down. It still unclear why CAR T cells travel CNS in the absence of disease. A report found that endothelial activation and blood brain barrier (BBB) disruption might contribute to CAR T-cell trafficking and CNS toxicity. Other studies indicated a role for myeloid cell activation in the CNS. Lastly, studies in mice showed that blocking IL-1 with anakinra, neurologic toxicity & CRS were eliminated(15).**Factors contributing to CAR T-cell toxicity**

Determinants of CAR T-cell toxicity include patient-related factors as ALL, disease burden, baseline low platelet

count, and baseline elevated markers of endothelial activation, and therapy specific factors as high CAR doses and fludarabine based -conditioning regimens (13).

GRADING OF CRS AND ICANS

The variations in toxicities grading among institutions exposed the importance to promote a common grading system for CAR T–cell-related toxicities. The American Society For Blood And Marrow Transplantation (ASBMT) published the ASBMT Grading System for CRS(Table 2) and ICANS (Table 3)(16).

Table 2. ASBMT CRS Consensus grading (16)

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38°C			
Hypotension	-	Not demanding vasopressor	± vasopressin	Demanding vasopressors (Not vasopressin)
Hypoxia	-	Demanding low-flow nasal cannula or blow-by	Demanding high-flow nasal cannula, non-rebreather mask, or Venturi mask	Demanding positive pressure

Table 3. ASBMT ICANS Consensus grading (16, 17)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	-	-	Any clinical seizure that rapidly resolves or non-convulsive seizures on EEG which resolves with intervention	Life-threatening prolonged seizure (> 5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	-	-	-	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	-	-	Focal edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Indications of CAR in ALL patients

The FDA approved the use of Tisagenlecleucel for ALL treatment. It was approved based on a study involved 63 relapsed or refractory B - ALL patients (18).

Uses of CAR-T cells includes relapsed cases who have failed many previous regimens, as hematopoietic stem cell transplantation or blinatumomab, patients with positive Philadelphia chromosome disease, those with refractory ALL, cases with Down syndrome and in patients with extramedullary disease (19).

Data concerning use of CAR T cell therapy in treatment of patients with CNS disease is limited. However, CAR-T cells can cross the BBB resulting in CNS remissions is a critical observation (20).

The future of CAR cell therapy for ALL

Full potential optimization still the main challenge for this therapy. The Limitation of CD19 positive relapses could be achieved by a good understanding for the biology of persistence. Limiting the presence of a negative CD19 clones might be defeated by manufacturing binary targeted CARTs. New targets as CD22 has shown to be a new effective target in B-cell ALL (21).

Conclusion

CAR T cells have dramatically improved the immunotherapeutic treatment of cancer: Great results related to hematolgical cancers have been accomplished. Neurotoxicity and CRS remain the barrier for widely use of this therapy.

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