A feasibility study comparing car-t cell therapy and separate limb end perfusion therapy in the treatment of melanoma

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Abstract. There are several potential advancements within cancer immunotherapy, but cells of chimeric antigen receptor-T stand out. Recently, two CAR-T cell designs targeting CD19 have been approved for use in the US and the European Union due to their promising results in the treatment of hematologic malignancies. Currently, researchers are focusing on evaluating the efficientness of CAR-T cell treatment for a variety of cancer of the solid tissues. Melanoma is caused by the malignant transformation of melanocytes. In addition to the skin, melanomas can also develop in other locations where neural crest cells migrate, such as the digestive system or the brain. Melanocytes are formed in the neural crest. Since transformed cells must overcome extra obstacles to survive, the treatment of solid cancers with cells that produce CAR-T has been less successful than the treatment of hematologic malignancies with cells that produce CAR-T. A solid cancer's immunosuppressive microenvironment and the inability to migrate cells that produce CAR-T to the site of the cancer are two significant barriers. In addition, finding the optimal target antigens to avoid on-target toxicity and non-cancer toxicity is a challenge. To lessen the harmful effects of systemic chemotherapy, Creech & Krementz developed isolated limb perfusion in 1956 to create high levels of chemotherapy in limbs affected by unresectable cancers, particularly soft tissue sarcomas and melanomas. By using these targets, it is possible to remove the wounded limb's circulation from the body's circulation and connect it to an extracorporeal system. When the patient becomes excessively hot, chemotherapeutic medications, primarily melphalan & cancer necrosis factor, are administered via a perfusion circuit. The objective of this article is to provide a summary of the benefits and drawbacks of employing car-t-cell therapy to cure solid cancers, particularly melanoma. It also investigates the possibilities of curing melanoma using car-T treatment as well as isolated limb perfusion.

Keywords: Car-t Cell Therapy, Isolated Limb End Perfusion Therapy, Melanoma.

1. Introduction

Melanoma incidence is rising all across the world. Melanoma is known to be prone to UV exposure. It is well established that geographic location affects the distribution of UV exposure and melanoma incidence [1]. According to epidemiological statistics, the distribution of melanoma on the body's surface and the histological features of lesions may also be influenced by gender and heredity. Melanoma has been treated with surgical excision, radiation, chemotherapy, targeted treatments, and several immunotherapies.

While still receiving therapy, metastases might appear in up to 5% of malignant melanoma patients. Surgical excision is often the first line of treatment, however, local area treatment approaches like isolated limb perfusion (ILP) are an option in cases when this is not practical [2]. cancer necrosis factor-alpha was authorized in Europe following a multicenter trial for locally advanced soft tissue sarcoma that was found to be incurable by an independent review board. 71% of patients had successfully isolated limb perfusion with TNF and Murphalan, and these patients still had their limbs. Several trials have shown that infusions of TNF and Murphalan into the limbs of patients with a range of limb-threatening cancers, including skin cancer or osteosarcoma resistant to chemotherapy, can be effective in treating these cancers. Isolated limb perfusion models have been employed in laboratories to understand the disease's mechanisms and develop novel treatments. Adding TNF to perfusion increases cancer uptake of film or adriamycin by a factor of three to six. They have also noticed that TNF has detrimental effects on the cancer vasculature. New vasoactive substances and methods of

action are continuously being discovered. An adenoviral vector is used to control isolated limb perfusion, which is a type of gene therapy that works well.

A large number of T lymphocytes are present inside the bodies of cancer patients. It makes it challenging for them to differentiate between healthy and cancerous cells. It is therefore possible for cancerous cells to camouflage themselves and remain undetected. In order to address this issue, cells that produce CAR-T were developed. In comparison with T cells, cells that produce CAR-T provide a very effective and long-lasting therapeutic response [3]. When a patient receives chimeric antigen receptor T-cell treatment, T cells are collected from their blood and are modified in a laboratory to produce synthetic receptors that target cancer antigens specifically. These do not utilize the major histocompatibility complex and instead detect cancer antigens directly [4]. Leukocyte isolation, also known as an isolated single collection of the patient's peripheral blood, is the first step in this treatment. The medical staff takes blood samples of T-cells (mono-collection). T-cells may be modified in a laboratory. The CAR T-cells have a new name: CAR T-cells. CAR stands for Chimeric Antigen Receptor. These CAR T cells are designed to seek out and attack certain proteins on cancerous cells. In the lab, these altered T cells develop and proliferate. Once a sufficient number of cells, the patient receives a single drop into their bloodstream. Finding and eliminating cancerous cells is the target of CAR T cells.

The fact that cancer may develop resistance to CAR constructions that only target one antigen is among the most challenging aspects of CAR-T cell therapy. And although cells that produce CAR-T that are directed at a single antigen may have excellent response rates, many patients who get treatment with these cells see their cancers stop being able to produce the targeted antigen. In the field of science, this is referred to as "antigen escape." Contrary to hematologic malignancies, cancerous cells have physical boundaries, including the cancer mesenchyme, that prevent cells that produce CAR-T from entering them. This is due to the microenvironment of the cancer inhibits the immune system. Since CAR-T cell therapy may result in severe adverse effects and even death, it has not yet been utilized as a first-line treatment. The severity and frequency of CRS, HLH/MAS, and/or ICANS events may depend on a variety of significant factors. These factors include the process used to create the CAR, the target, and the kind of cancer.

2. The causes of melanoma

2.1. The structure of BP neural network

Although the cause of melanoma is uncertain, it is believed to be linked to ultraviolet radiation exposure, possibly years before the cancer manifests itself. Malignant melanoma may have grown due to various reasons, such as more people engaging in outdoor leisure activities, shifting employment patterns, and the use of skin-exposed clothes. At least one first-degree or second-degree relative with a familial type of melanoma have been diagnosed with moles or melanomas. These people have a lifetime chance of melanoma development of almost 100%. Others have pale skin, a high number of moles, and a history of excessive sun exposure as children (including sunburn).

3. Treatment

3.1. Treatment of melanoma is the surgical removal of the primary cancer

Melanoma, which accounts for just around 5% of all skin malignancies, is the cause of the majority of skin cancer-related fatalities. Surgery has become an important part of the management of patients with advanced illnesses, but it is also the primary treatment for patients with localized diseases. The proportion of individuals who survive five years with local lymph nodes & distant metastases is around 60% and 5%, respectively. Early identification enables curative resection, and the five-year survival rate for all stages of melanoma is 91% [5]. In terms of surgical excision of melanoma metastases to the GI tract, data supplied by the American College of Surgeons indicate that surgical

intervention for symptomatic relief with minimum morbidity and mortality is possible for nearly all patients suffering from melanoma & GI metastases. To find out if surgery might help people with GI metastases of melanoma live longer, In the selection process, 124 candidates with metastatic melanoma affecting the rectum, small intestine, colon, or stomach were identified. Before being diagnosed, these people had been disease-free for a median of 23.2 months (ranging from 1 to 154 months). Symptomatic masses, crampy stomach pain, and/or unexplained gastrointestinal blood loss were the most common patient complaints. Of the 124 patients, palliative surgery was performed on 23 (34%), radical resection on 46 (66%), and abdominal surgical exploration on 69 (55%) individuals. 67 of 69 (97%) individuals who underwent surgery experienced postoperative relief from gastrointestinal problems; there was only 1 operative fatality and 1 significant surgical complication. In contrast to patients who underwent palliative surgery and nonsurgical treatments, the median survival period for patients who had radical resection was 48.9 months, which was longer than the 5.4 to 5.7 months range. It is suggested that people with this type of melanoma and a disease that has spread far away should carefully consider surgery.

The first drawback of surgical melanoma treatment is that when extensive excision is utilized, the cancer site and a small piece of healthy skin surrounding the margins are removed. The wounds are then typically sutured together, which might outcome in scarring. A wider margin is frequently needed to achieve complete histologic clearance because in situ melanoma (MIS) frequently exhibits subclinical extension, especially in the malignant freckle (LM) subtype. The majority of current international clinical guidelines call for a clinical margin of 5–10 mm for MIS excision. Before sophisticated reconstruction or tissue rearrangement, histologic clearance should be validated if there is clinical suspicion that the risk of subclinical spread is significant. The second point is that, in the rare event that a finger or toe is involved and the melanoma has spread extremely deeply, amputation of all or a portion of the finger may be necessary. Along with discussing the necessity of the act of amputation itself and developing criteria, it is important to consider the difficulties of postoperative care and the patient's rehabilitation due to the amputation. The third argument is that surgery is unlikely to be able to treat melanoma if it has metastasized, or spread, from the skin to other organs like the lungs or brain. Imaging procedures like CT or MRI scans may only be able to detect 1 or 2 locations of spread; there may be more places that are too small for them to pick up.

3.2. Treatment of widespread disease consists primarily of chemotherapy-based regimens

Chemotherapy used to be the main course of treatment for metastatic melanoma prior to current medical advances. For metastatic melanoma, DTIC has been considered the gold standard therapy since 1972, and it has been shown to have meaningful effects in some patients. In the liver, 5-methyl-1-triazine imidazole-4-carboxamide must be converted into its active ingredient, 5-methyl-1-triazine imidazole-4-carboxamide [6]. biochemical treatment using recombinant interferon-a and/or interleukin-2. With very few exceptions, none of these treatment plans have, however, led to the condition being effectively controlled over the long term. Comprehensive investigations looked into several chemotherapy regimens to prolong the effects of single-agent dacarbazine, but they failed to find any improvement in overall survival [7]. Combining carboplatin and paclitaxel led to objective reactions resembling those of dacarbazine as a single drug. Biochemotherapy, which combines immunotherapy and chemotherapy, has a strong clinical response.

4. Perfusion of isolated limbs in the treatment of melanoma has both advantages and disadvantages

Melanoma that has spread to the limbs may be treated with cytotoxic medications rather than by administering infusions to the isolated limbs. It is less intrusive and more efficient. Catheters are inserted percutaneously into the axial vein as well as the artery of the afflicted leg to stop blood flow to the proximal limb. Since the diseased limb is isolated from the rest of the body, targeted intra-arterial chemotherapy is easier to administer. Between 1997 and 2007, 20 patients who were chosen

for one or more surgical operations underwent 28 ILI procedures using the ILI technology, which was developed by the Australian Institute of Melanoma Research. During the follow-up period, which would be 15.9 months following the onset of the first ILI, "clinically significant" response rates of 90% and a 70% rate of overall response, 35% complete responders, 35% partial responders, and 20% stable illness were determined. A total response rate of 70% was reported after one ILI (n is equal to 20), with 20% reporting a full response, 50% reporting a partial response, and 20% reporting a stable condition. Amputation was not necessary in most cases, and little limb toxicity was observed.

Treatment options for localized limb melanoma recurrences include removing the affected limb, ablation with lasers, injections locally, cryotherapy, and vaccine treatment. Nevertheless, there are limitations to these alternatives when there are numerous or large metastases, and systemic chemotherapy, radiation therapy, or other treatments should be considered. Due to the possibility of systemic side effects, standard systemic chemotherapy can only be administered at lower doses. However, if the damaged leg is vascularly "separate" from the circulation, greater chemotherapy dosages may be administered [8]. In spite of this, it poses a substantial risk of morbidity and death due to its invasive nature. In addition to arterial dissection and clamping, extracorporeal bypass pump circuit usage is necessary. Response rates varied between 71% and 88% on the whole. for isolated limb perfusion. Changes in patient selection criteria may account for the variation in full remission rates between studies. The most common complications associated with solitary perfusion of the limb consist of compartment syndrome of the facial area, neuropathic pain, infectious complications, as well as arterial or venous thrombosis.

There were twenty patients who had [8]. The Royal Adelaide Hospital underwent LI procedures between July 1997 and May 2007. On 15 patients, one ILI procedure was conducted; in the case of two patients, 2 ILI operations were performed; while on 3 patients, three ILI operations were performed. There was an overall remission rate of 70% after the previous ILI, with a full remission rate of 35% (n is equal to 7) as well as a 35 percent remission rate in partial remission (n is equal to 7). In 10% of cases (n is equal to 2), the illness progressed, while in 20% of cases (n is equal to 4), the disease was stable. When stable disease is considered, "clinically significant" response rates are approximately 90%.

A more intrusive and expensive operation is not necessary when ILI is used to treat metastatic limb melanoma, according to recent clinical data. Future research may benefit from combining ILI chemotherapy with other systemic treatments. ILP-related quality of life issues and chemotherapy-related adverse effects like toxicity are the key concerns for patients receiving this treatment. A total of 292 patients with melanoma of the extremities were treated at the Antoni van Leeuwenhoek Hospital in Amsterdam, the Netherlands, between 1978 and 2001. 59 of them were healthy and still vibrant when they took part in the research. The majority of the patients were female, and they were 57 on average. The average number of years because ILP was 14 [9]. The findings demonstrated that a variety of disease-related and/or ILP-associated symptoms could be experienced by long-term survivors and may have an impact on their life quality. For example, 15% of patients experience significant acute toxic reactions (such as edema and blistering) in their limbs, which may cause long-term functional damage.

5. Car-T Cell Therapy for Hematologic Malignancies

A malignant blood condition called acute lymphoblastic leukemia (ALL) is characterized by aberrant primitive cells in the bone marrow and excessive primitive cell growth [10]. The most effective treatment for ALL, particularly the lethal r/r B-ALL, is CAR-T cell therapy, which has demonstrated impressive success. Before allogeneic HSCT, CAR-T cell treatment can be utilized in patients with resistant malignancies to lessen cancer burden or potentially induce remission. As a result, allogeneic HSCT success rates may be improved. Patients with recurrent B-cell cancer after allogeneic HSCT, especially those with B-ALL, may benefit more from CAR-T cell therapy than donor lymphocyte infusion.

6. Melanoma CAR-T cell therapy's effectiveness and limitations

6.1. Effectiveness

The short treatment duration of CAR T-cell treatment is one of the greatest advantages. A maximum of two weeks of inpatient care may be necessary for a single infusion before it is finished. Most patients recover far more quickly than they would following a stem cell transplant using harsh chemotherapy because it is not employed in this procedure despite the fact that CAR-T therapies are not currently permitted for solid cancers [11]. However, studies on people with blood cancers have shown that CAR T-cell treatment may lead to remissions lasting for a long time, even if the cancer returns after taking a number of medicines. Others can experience extended cancer-free survival times and, in some situations, gain from curative cancer therapies such as stem cell transplants. Cells that produce CAR-T have a long shelf life, which is an advantage when using patient-specific T cells for the production of medicine. In the event of a recurrence, these cells may recognize and target cancerous cells because of how long they may survive in the body. According to studies, targeted treatments or immunotherapy may be beneficial for 50% or more of patients with stage IV cutaneous melanoma, and surface melanomas express HER2 at varying degrees in vitro and react to HER2 cells that produce CAR-T [12]. Additionally, cancerous cells in the body that resist TIL treatment may be able to be eliminated by HER2 cells that produce CAR-T.

6.2. Effectiveness

The efficientness of CAR-T therapy for patients suffering from solid malignancies is directly impacted by difficulties associated with cells that produce CAR-T, which is required to first migrate towards the cancer [13]. As modified T cells must leave the vasculature and traverse a chemokine gradient to reach the malignancy, this describes a physical barrier. cells that produce CAR-T must battle in the hostile cancer microenvironment after extravasation (TME). cells that produce CAR-T are unable to successfully eradicate cancerous cells due to anti-inflammatory cytokines generated by regulatory T cells and other immune cells, as well as inhibitory receptors increased on TME-modified T cells. Identifying the optimal antigens to assault is another issue that often arises with CAR-T cell therapy [14]. It is crucial to select antigens that are primarily present on cancerous cells to prevent recognizing healthy tissue. Once the optimal cancer-associated antigen has been identified, another challenge is to overcome loss of antigens due to immune system hiding mechanisms. CAR-T cells don't function effectively in solid cancers since they are exhausted before the cancer is removed, due to environment within the cancer, or since the antigen isn't produced consistently, according to what is known about how common T cells are switched off by cancer. The CAR-T cell treatment has the following effects: Cytokine release syndrome has been linked to allergic reaction (neurological side effect) greater potential for infection high levels of uric acid in the blood as an outcome of cancerous cells dividing fast (lysis of cancer).

Table 1. Different new strategies and ways of dealing with these problems table

Treatment method	Advantages	Disadvantages
Car-t cell therapy	1. Short treatment period 2. Has a long shelf life 3. Can receive targeted therapy or immunotherapy	1. Physical barrier to the movement of cells that produce CAR-T to the cancer 2. cannot successfully eradicate cancerous cells 3. Difficulty in finding the best target antigen 4. Depleted before reaching solid cancers

Perfusion of isolated limbs	1. A minimally invasive procedure that is effective. 2. It is common for lower extremity toxicity to be noticed and does not require amputation. 3. It may be used in conjunction with an authorized or investigational systemic treatment.	1. Membrane compartment syndrome, neuropathic pain, infectious diseases, and arterial or venous thrombosis. 2. It is a complex and expensive procedure.

7. Possibility of car-t cell therapy combined with isolated limb perfusion

Since ILI can get to the site of action and deliver high concentrations of the drug to the site of melanoma, it may be a good and workable solution to the problems with carcinoid cell therapy in solid cancers, which are that it is hard to get to the site of action and the drug is used up before it gets to the solid cancer [15]. Furthermore, therapy of car-t cell has advantages in terms of the therapeutic cycle as well as targeting of cancerous cells, thus allowing the inference of a possible combination of the two. There is a lack of experimental data to combine the two, as well as a lack of theoretical basis as no extensive literature on relevant experiments, was found.

8. Conclusions

Isolated limb infusion is a highly effective treatment for limb metastatic melanoma, comparable to chemotherapy regimens delivered by isolated limb infusion, without the need for more invasive and expensive surgery. In addition to its low morbidity rate, ILI is relatively easy to administer [16]. It has been reported that the U.S. FDA has approved six CAR T-cell treatments to treat blood malignancies, namely lymphoma, leukemias, and more recently, multi-nodular myeloma [17]. There has been considerable success with the treatment of carcinoid cells. to eradicate very advanced leukemias and lymphomas, and years to stop cancer. Both have proven benefits over conventional surgery or chemotherapy medications for the treatment of cancer, and there is the possibility of using both in tandem.

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