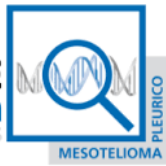

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Bibliographic review First semester 2021
Elisa Roca (elisaroca@gmail.com)

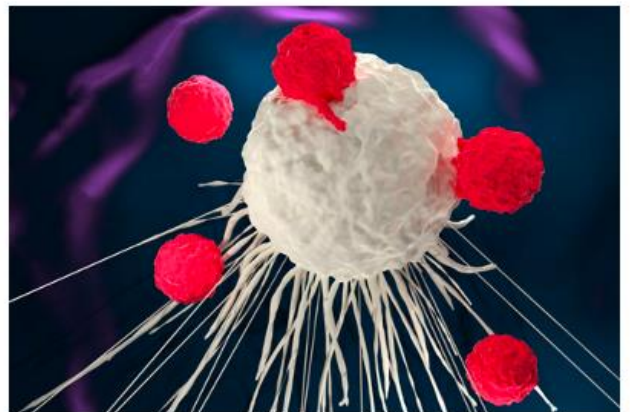
New therapeutic strategies for Malignant Pleural Mesothelioma: CAR T cells

Introduction

As we all know, malignant pleural mesothelioma (MPM) is an aggressive neoplasia that does not respond well to the standard treatment currently being used in clinical practice and that has a bleak prognosis. Nevertheless, new immunotherapeutic approaches are currently being tested and, specifically, there is some data regarding the possibility of developing therapies aimed at specific targets. One of these is the tumor-associated antigen mesothelin.

Within this framework, new therapeutic strategies are being developed such as the possibility of using laboratory-designed CAR T cells that are able to target mesothelin. The following bibliographic review aims at compiling literature data concerning the application of the CAR T therapeutic approach to malignant pleural mesothelioma, considering this treatment strategy as a future perspective for improving the prognosis and outcomes of patients suffering from this neoplasia.

We will therefore attempt to provide some answers to simple questions that the reader may have when dealing with these complex issues but aimed at therapeutic innovation with regard to Malignant Pleural Mesothelioma.



From the Internet Illustration:
CAR-T cells attacking a cancer cell

Mesothelin

Mesothelin (MSLN) was discovered in 1992 in an effort to find new surface targets for immunotherapy through the application of monoclonal antibodies.

It is **expressed** at low levels in healthy mesothelial cells of the pleura, pericardium, and peritoneum, while ideally any neoplastic tissue of MPM might show a notable expression of MSLN.

The **physiological role** of MSLN in healthy tissues is currently not fully understood. MSLN is initially expressed as a 71-kDa protein, which is then cleaved by furin, causing the release of a 31-kDa protein, called Megakaryocyte Potentiation Factor (MPF), while the remaining 40-kDa fragment stays attached to the cell membrane through a glycosylphosphatidylinositol (GPI) anchor.

Mesothelin (MSLN) maturation

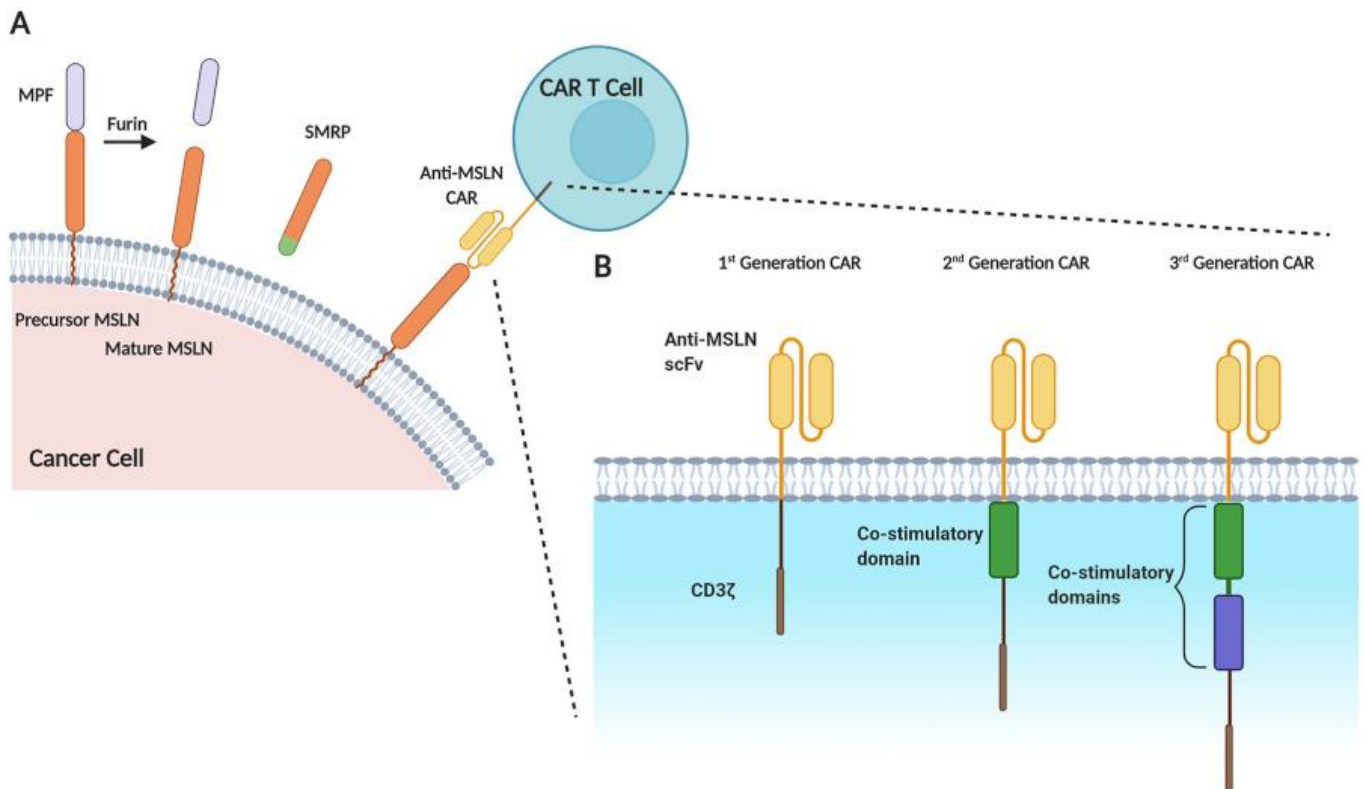


Image taken from an article by Castelletti et al. Biomarker Research (2021)

Surface MSLN may also be released by creating Soluble Mesothelin-Related Peptide (SMRP), which can likewise be detected in the blood of patients affected by MPM.

MSLN has been the focus of **immunotherapy** research ever since it was discovered. The characteristics that make MSLN an ideal immunotherapeutic target in MPM are many, but they can be summed up as follows:

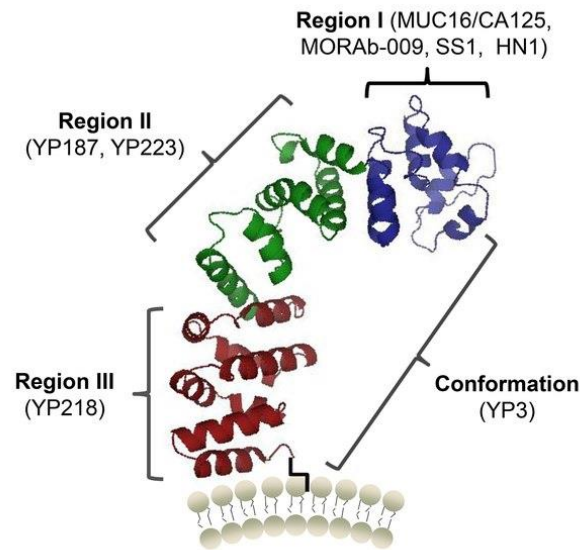
- a high level of MSLN expression in the cancer tissue and low or no expression in healthy tissue, thus minimizing possible toxicities;
- 85 to 90% of cases in the MPM epithelioid subtype have high MSLN expression [12];
- its expression at high levels has been linked to increased aggressiveness and invasiveness.

MSLN is made up as follows.

The extracellular domain of MSLN includes three adjacent elements:

1. region I (residues 296-390),
2. region II (391-486),
3. region III (487-598).

Region I is the distal part of the membrane and can bind to MUC16 mucin (also known as CA125), which is also expressed by most MPM cells and is linked to neoplastic aggressiveness characteristics. This MSLN-MUC16 interaction has proven to be of great significance for tumor cell adhesion and metastasis and is the primary target of current immunotherapies, including CAR T cell therapy.



A model of protein structure of human mesothelin

CAR T CELLS

What are cellular therapies?

Cell therapy uses hematological cells (obtained from blood) genetically modified in the laboratory through specific molecular engineering methods. To proceed with these genetic approaches, highly complex instruments as well dedicated and well-equipped laboratories are needed. The cells, suitably engineered, can be injected into the diseased organism, where they can perform the desired and intended therapeutic action.

What does CAR stand for?

CAR is an acronym used to indicate chimeric antigen receptors, also referred to as chimeric immunoreceptors or chimeric T-cell receptors or engineered T-cell receptors. Essentially, these are receptor proteins designed to give T lymphocytes the new ability to detect a specific protein target. The receptors are called "chimeric" because they combine both antigen-binding and T-cell activation functions in a single receptor.

What are CAR-T cells?

Hence, CAR T cells chimeric antigen receptor cells and are genetically modified T lymphocytes. The main objective of engineering these cells is to produce an engineered T-cell receptor, which is used in the treatment of certain hematological neoplasia. This is, therefore, a powerful example of the clinical efficacy of cell therapies, which produce CAR-T cells "genetically trained" to search for, recognize and eliminate neoplastic cells.

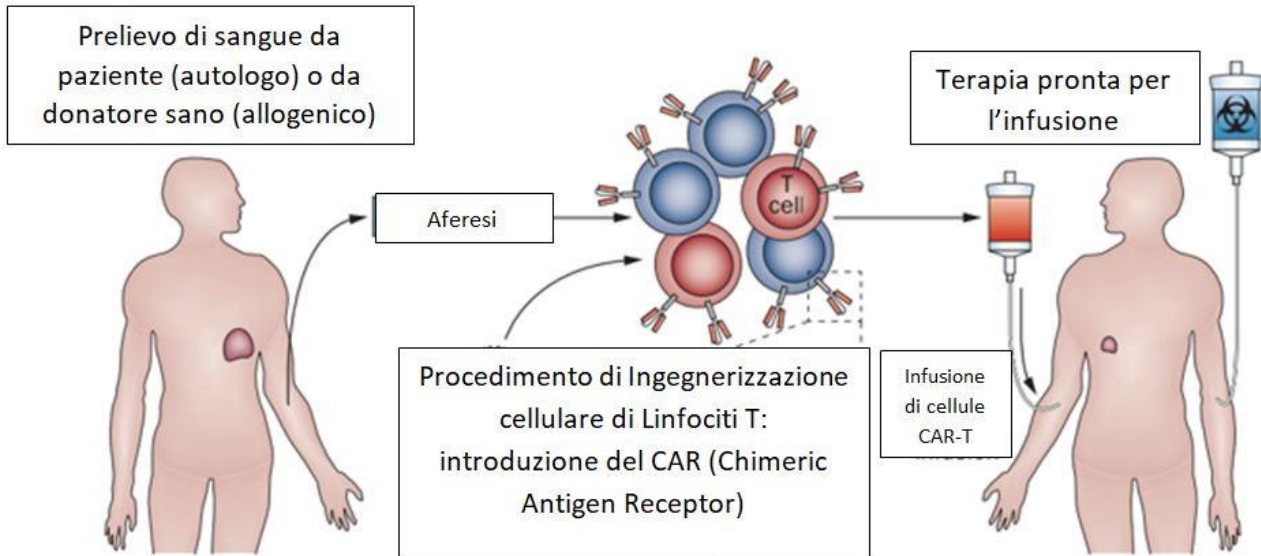
How are CAR-T cells produced?

The production of CAR-T cells is extremely complex.

The first step consists in taking a blood sample from the patient, which is then processed in a lab in order to separate the cellular material (blood cells) from the plasma, using a technique called apheresis. This procedure makes it possible to collect and isolate the patient's lymphocytes. These cells are then sent to laboratories specialized in engineering according to well-defined scientific protocols.

Once the T cells have been isolated, the CAR (Chimeric Antigen Receptor), which is capable of recognizing cancer cells, is introduced. In fact, these T lymphocytes, defined at this point CAR-Ts, express a surface receptor

that detects specific antigens expressed by neoplastic cells.



What does CAR-T therapy consist of?

Generally speaking, we can say that **CAR-T therapy** uses T cells engineered with CAR, the therapeutic approach for some neoplasia. The rationale for this treatment application is the ability of CAR T cells to modify T cells so that they can recognize the tumor and, consequently, attack and fight it in the most effective way possible.

This treatment is completed starting from the patient's blood, which is drawn and processed in the laboratory, leading to the extraction of T cells. These cells, after being suitably isolated, are then processed using a vector, which usually consists of a modified lentivirus, so that they can express a defined CAR that guides them towards a specific tumor antigen. It is crucial that the CAR T cells be designed as being specific for antigens that are typical of neoplastic cells and that are not as present in healthy tissues, in order to develop a treatment that is as effective as possible, but also as non-toxic as possible. After such treatment, the cells thus modified can be reinfused into patients with neoplasia. In particular, CAR T cells can be defined as:

- autologous, if obtained from the patient's own T cells,
- allogenic, if obtained from a healthy donor.

CAR-T cells destroy neoplastic cells through a variety of mechanisms, among these they are able to increase the degree of toxicity (cytotoxicity), they can contribute to increased secretion of factors affecting cytokines, interleukins and growth factors. Precisely because of this action, one the side effects of the therapeutic application of CAR-T cells is the so-called "cytokines storm", which can create serious damage, related to cytokine activation and other factors such as tumor volume and the patient's specific pathophysiological state. This adverse reaction usually takes place in the first days after therapeutic administration and is often treated with corticosteroids and IL6 inhibitors (tocilizumab).

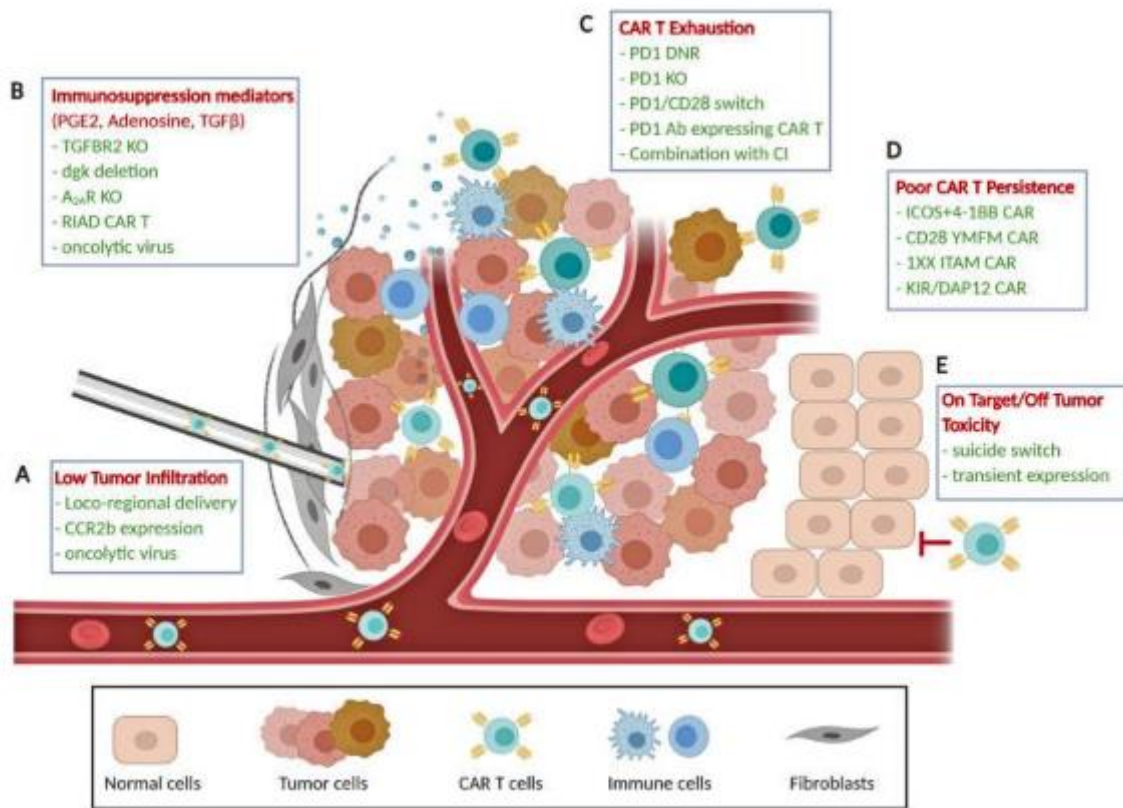


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CAR-T therapy and Malignant Pleural Mesothelioma

CAR-T cells used against malignant pleural mesothelioma are T lymphocytes engineered to target mesothelin. As we know, CAR-T cell therapy is effective in the treatment of hematologic neoplastic diseases, whilst applications known to date for solid tumors are limited.

In 2019, during the conference held by the American Association for Cancer Research (ASCR), a number of scientists presented encouraging results against this type of thoracic cancer, targeting mesothelin and using CAR-Ts specific for this target.

Initial results from a phase I study (trial) were presented in March 2019 at the annual meeting of the American Association for Cancer Research (Abstract CT036) and again in the Journal of the American Society of Clinical Oncology (ASCO – Abstract 2511).

Briefly, these were the results of this preliminary study: 21 patients with malignant pleural disease (19 MPM, 1 lung cancer, 1 breast cancer) were treated (40% had received ≥ 3 lines of prior therapy). 18 patients received preconditioning with cyclophosphamide; the first cohort did not receive cyclophosphamide. CAR T cells were administered to twelve patients using an interventional radiology procedure. One patient had grade 3 cyclophosphamide-related febrile neutropenia, whereas no CAR T-cell-related toxicities above grade 2 were observed. The last cohort of patients was hospitalized 2 weeks after infusion with a temperature of $>38^{\circ}\text{C}$ and fatigue. Intensive monitoring of toxicity carried out through clinical evaluation (chest or abdominal pain), radiological evaluation (CT/PET or echocardiogram for pericardial effusion, ascites), laboratory evaluation (troponin elevation), and other evaluation (electrocardiogram) documented no toxicity. One patient underwent

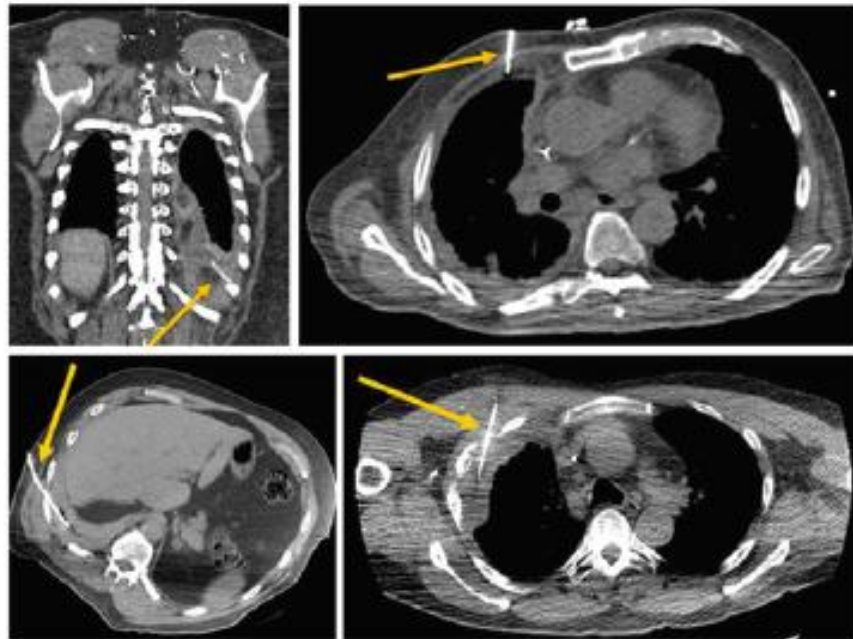
successful surgical resection for treatment purposes 6 weeks after infusion of CAR T-cells. CAR T cells were detected in the peripheral blood of 13 patients (from day 1 to week 38). T-cell persistence was associated with decreased serum levels of serial soluble MSLN-related peptide (>50% compared with pretreatment) and evidence of tumor regression on imaging studies. Once lack of toxicity was confirmed (6-17 weeks after CAR T-cell infusion), 14 patients were treated with immunotherapy and received anti-PD1 checkpoint blocking agents (1-21 cycles) without toxicity. The best response among the 19 MPM patients (13 patients received an anti-PD1 agent; PD-L1 <10% in all but 1) was achieved by 2 patients who had a complete metabolic response at PET (60 and 32 weeks ongoing); 5 with partial response; and 4 with stable disease.

A few months later, at the European Congress of Medical Oncology (ESMO - Barcelona), the first results of a phase I study using CAR-T cells in three patients with malignant pleural mesothelioma were presented. It was a study limited to very few patients, in fact, conducted on just three patients with malignant pleural mesothelioma, but it represented a new possible path to take against this disease.

Alessandra Curioni Fontecredo, Italian researcher and Head of the Thoracic Tumor Unit at the Department of Oncology and Hematology at the University Hospital of Zurich, talks about her research in this regard and in an interview comments on her study saying: "...we administered CAR-T, developed in partnership with the University of Zurich, to three patients with pleural mesothelioma in a phase I study. The chimeric receptor used, "assembled" on T lymphocytes and able to recognize tumor cells, targets a molecule known as FAP, an acronym for Fibroblast Activating Protein. This molecule is expressed in many epithelial tumors, such as those of the colon or ovary, and is often present in particular in mesotheliomas: it is found in about 80% of cases. The idea of starting precisely from mesotheliomas is that, in this case, researchers can proceed with a local therapy, with the injection of CAR-T cells directly in the thoracic cavity. We can't say anything about the efficacy of the therapy, also because the patients involved in the study underwent chemotherapy before and after the administration of CAR-T cells. However, from a safety standpoint we found no serious side effects or toxicities related to the infused cells. Of the three patients treated, one is alive at one year after the treatment and another at two years. At the moment this study, the first in Europe as regards solid tumors, was stopped, but we are working to optimize the chimeric receptor, for example through the addition of other stimulation molecules, and we hope to start a new trial next year."

A new therapeutic scenario for malignant pleural mesothelioma has opened up from these insights, and several studies have been proposed in the scientific field in an attempt to confirm this data and elaborate on these findings. Should the reader be interested, please refer to the bibliography provided at the end of this review.

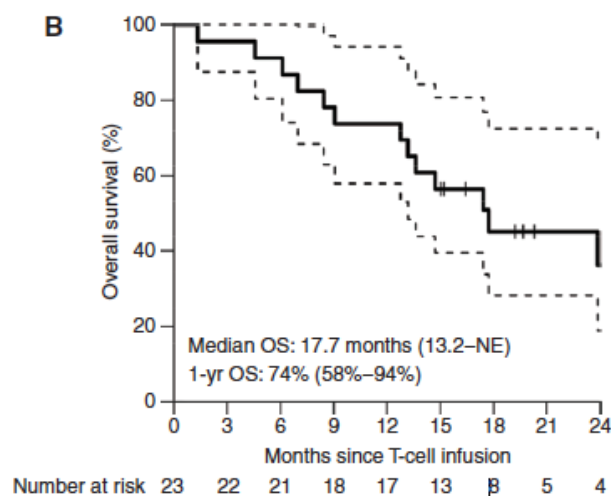
In this bibliographic review we like to mention in particular one of the latest researches on this topic.



The administration was carried out by injecting the therapy through a pleural catheter already in place, or by means of interventional radiology methods.

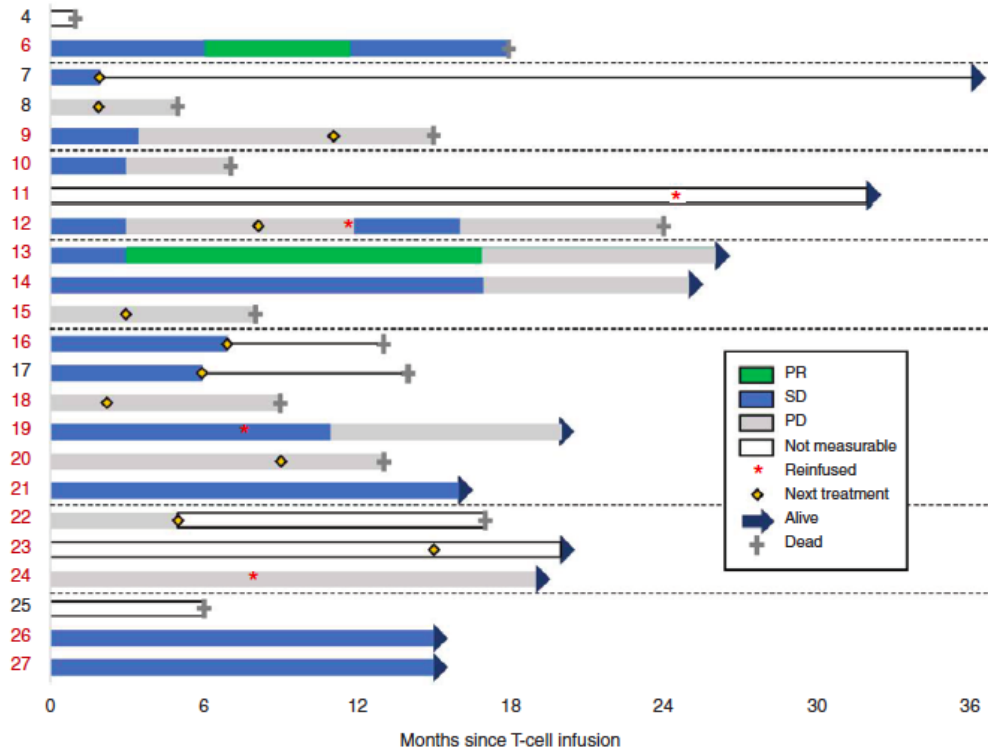
CAR T cells were detected in peripheral blood for >100 days in 39% of patients.

Previous studies had documented the possibility to combine CAR-T therapy with immunotherapy, already known and widely applied to thoracic neoplasia. More in detail, these experimental studies, conducted on mice, had shown that PD-1 blockade improves the function of CAR T cells in mice. Starting from this preliminary data, a human study was designed to associate pembrolizumab (immunotherapeutic monoclonal antibody) to CAR-T therapy. This trial took place in 18 patients with mesothelioma: among these patients, median overall survival from CAR T cell infusion was 23.9 months (overall survival at 1 year, 83%).



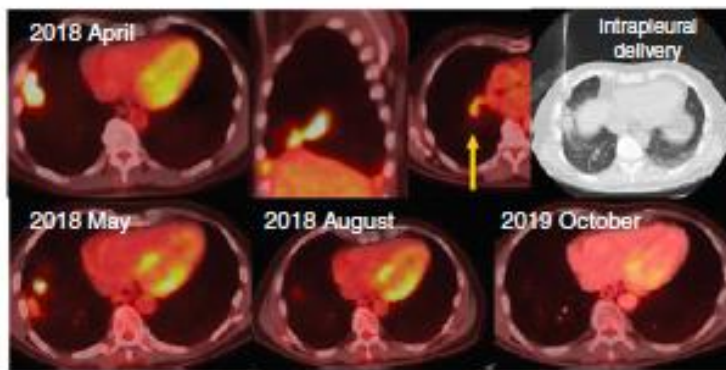
The graph represents the survival of patients with malignant pleural mesothelioma treated in this study. Stable disease was maintained for ≥ 6 months in 8 patients; 2 patients showed a complete metabolic response

on PET. Therefore, the researchers emphasized in this study how the data supports the study of immunotherapy combined with CAR T cells and PD-1 blocking agents in solid tumors.



The graph represents the outcomes from patients affected by MPM treated in this study (PR = Partial Response, SD = Stable Disease, PD = Progression Disease.)

The following photographs show practical examples of treatment response in patients with mesothelioma.





Researchers concluded that the local administration CAR T-cell therapy targeting mesothelin followed by the administration of pembrolizumab is feasible, safe, and shows evidence of antitumor efficacy in patients with malignant pleural disease.

Conclusions

The study of CAR T cells made it possible to analyze their application not only for hematologic diseases, but for solid tumors as well.

Among these, malignant pleural mesothelioma has become a potential target of these treatments.

Specific cells of the immune system suitably engineered, become effective against specific targets and, if these targets are found on the neoplastic cells of malignant pleural mesothelioma, then it is possible to develop well-defined therapeutic strategies.

A new therapeutic approach in this innovative scenario for malignant pleural mesothelioma is represented by the application of CAR T cells. Preliminary results in this regard show interesting transversal implications and present encouraging future prospects.

Further dedicated studies will be able to confirm these researches and eventually bring into clinical practice new therapies for this pleural pathology.

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