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Immunotherapy - a review on the new horizons of cancer-fighting

Imunoterapia - uma revisão sobre os novos horizontes no combate ao câncer

Aldren Thomazini Falçoni Júnior[1], Bianca Savazzini Reis[2], Bruna Anchieta de Carvalho Zorzanelli[3], Carolina Izoton Sadovsky[4], Ednéa Zandonadi Brambila Carletti[5]

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ABSTRACT: *Introduction*: Immunotherapy is progressing to become an expressive tool in the fight against cancer, from manipulating the immune system of patients to eliminate tumors. Many institutions have invested in research in the field, since the immunotherapeutic approaches have advantages over conventional therapies, in addition to presenting potential for hitherto intractable cancers. *Objective*: To define some mechanisms based on immunotherapy, in addition to citing their classes and in which types of cancer these therapies have been used. *Method*: This is a literature review of the selection of articles from the last 10 years in the PubMed database with the keywords "Immunotherapy, Adoptive" combined with the term "Lymphocytes, Tumor-Infiltrating" and "Immunotherapy, Adoptive", combined with "Neoplasms". *Results*: The term immunotherapy represents a vast class of treatments based on the Immunity Cycle of Cancer Checkpoint. Inhibitors, for example, block immunosuppressive mechanisms performed by the tumor. In another instance is adoptive cell therapy, which consists of extracting and training T-lymphocytes from the patients themselves to identify and combat specific antigens of the tumor tissue. Also noteworthy are the vaccines, which use attenuated and genetically modified tumor cells to stimulate the immune response. These therapies are being studied in several types of cancers, showing encouraging results in melanomas, breast cancers, glioblastomas, hematologic cancers, like the metastatic myeloma, among others. In addition, the combination of immunotherapeutic techniques with conventional therapies is also a promising alternative. However, barriers to consolidating a more efficient and lower-cost production method still limit the mass use of some of these therapies. *Conclusion*: Many immunotherapeutic approaches are still experimental and their comprehensive application is still uncertain, however, the results obtained by the clinical studies demonstrate the exciting perspective for this new horizon in the fight against cancer.

Keywords: Immunotherapy; Neoplasms/therapy; Immunotherapy, adoptive; T-Lymphocytes.

RESUMO: *Introdução*: A imunoterapia caminha para se tornar uma expressiva ferramenta no combate ao câncer, a partir da manipulação do sistema imunológico dos pacientes para eliminar tumores. Muitas instituições têm investido em pesquisa na área, uma vez que as abordagens imunoterapêuticas apresentam vantagens sobre as terapias convencionais, além de apresentar potencial para cânceres até então intratáveis. *Objetivo*: Definir alguns mecanismos que baseiam a imunoterapia, além de citar suas classes e em quais tipos de câncer essas terapias têm sido utilizadas. *Método*: Trata-se de uma revisão bibliográfica feita por meio da seleção de artigos dos últimos 10 anos na base de dados PubMed com as palavras-chaves "Immunotherapy, Adoptive" combinado com o termo "Lymphocytes, TumorInfiltrating" e "Immunotherapy, Adoptive" combinado com "Neoplasms". *Resultados*: O termo imunoterapia representa uma vasta classe de tratamentos baseados no Ciclo de Imunidade ao Câncer. Os Inibidores de Checkpoint, por exemplo, bloqueiam mecanismos de imunossupressão realizados pelo tumor. Já a Terapia com Células Adotivas consiste em extrair e capacitar linfócitos T dos próprios pacientes para identificar e combater antígenos específicos do tecido tumoral. Destacam-se também as vacinas, que utilizam células tumorais atenuadas e modificadas geneticamente para estimular a resposta imune. Essas terapias estão sendo estudadas em diversos tipos de melanomas, cânceres de mama, glioblastomas e cânceres hematológicos, tal como o mieloma metastático, entre outros. Além disso, a combinação de técnicas imunoterápicas com terapias convencionais também apresenta-se como alternativa promissora. No entanto, barreiras na consolidação de um método de produção mais eficiente e de menor custo ainda limitam a utilização em massa de algumas dessas terapias. *Conclusão*: Muitas abordagens imunoterápicas ainda são experimentais e sua aplicação abrangente ainda apresenta-se incerta, contudo, os resultados obtidos pelos estudos clínicos demonstram a animadora perspectiva ao redor desse novo horizonte no combate ao câncer.

Descritores: Imunoterapia; Neoplasias/terapia; Imunoterapia adotiva; Linfócitos T.

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1. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - EMESCAM. Graduando em Medicina. Orcid: https://orcid.org/0000-0001-7350-4910. Email:aldrenf@terra.com.br.
2. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - EMESCAM. Graduanda em Medicina. Orcid: https://orcid.org/0000-0001-5042-2680. Email: biancareismed@gmail.com.
3. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - EMESCAM. Graduanda em Medicina. Orcid: https://orcid.org/0000-0001-7057-792X. Email: bruncarv@gmail.com.
4. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - EMESCAM. Graduando em Medicina. Orcid: https://orcid.org/0000-0001-5960-0156. Email: carolinasadovsky@gmail.com.
5. Instituto de Ensino Superior do Espírito Santo - Faculdade Multivix. Professor e Coordenador de Pesquisa e Extensão. Orcid: https://orcid.org/0000-0003-1252-0145. Email: edneab@gmail.com.

Endereço para correspondência: Aldren T. Falçoni Junior. EMESCAM - Avenida Reta da Penha, 2190, Santa Luiza. Vitória, ES. CEP 29045-402.

INTRODUCTION

Immunotherapy is an extremely vast class of treatments, which has drawn attention because of the rising number of pre-clinical and clinical trials demonstrating encouraging results. This new type of treatment shows an alternative to the patients with cancer on which the conventional therapies have not reached satisfactory results. The immunotherapeutic method's action mechanism basically has as its premise the enhancement and enabling of the patient's immunologic system, so it can recognize and combat the tumor cells, and capacitating said system to avoid the immunossupressant barriers created by the carcinogenic cells[1].

The essence of this strategy is to incorporate to the fight against cancer, cells that should have recognized the mutation of a specific group of cells and interrupted the abnormal mitotic proliferation before the tumor was formed. Therefore, the immunotherapeutic principle is based upon the phenomenon of immunologic vigilance carried out by effector cells, such as T cells, macrophages and *natural killer* cells, which can be tricked by the immunossupressant strategies of a tumor, leading to the development of cancer.

It is not rare for the immunotherapy to occur alongside other current treatments, since it focuses on the preparation of the tumor's immunologic ambient, aiming to potentialize the treatment strategy[2]. As a result, the treatment then combines the direct action of chemotherapeutics and radiotherapeutics with the active cooperation of the host body's defense cells, which have suffered modifications and stimuli to display a more intense and specific antitumoral action.

Among some of the properties of the immunotherapeutic treatment, its specific character must be highlighted. For instance, in therapies with transference of adoptive cells, the processing of the immunologic cells must aim to track and fight the specific antigens that are present in the patient's tumor cells[3]. With that goal, the individual's tumor tissue must be analyzed for the choice of the antigen with the highest specificity; it is visible the exercise of personalized Medicine. This concern warrants higher chances of success and prevents the destruction of healthy cells due to the ablation therapy. Reaching high levels of specificity has its advantages, since it spares non-tumor cells, increasing the therapy's positive results and diminishing collateral effects that compromise the patient's quality of life.

However, the use of immunotherapy is not applied to all types of cancer, for it depends on some requisites. Moreover, it is important to highlight that there are cancers in which this new methodology still has not been tested.

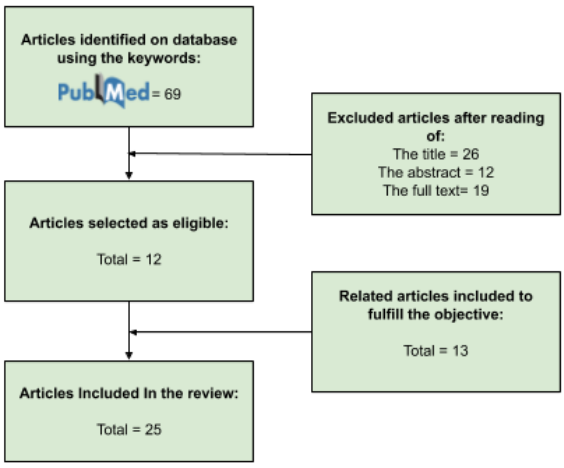
Thus, the objective of the present study is to define some mechanisms that base immunotherapy, citing its classes and in which types of cancer this treatment has been used.

METHOD

The research was made on *Pubmed* database, evaluating articles published in the last ten years (2008-2018). The terms used for the initial selection on Pubmed were: *"Immunotherapy, Adoptive"* [Mesh] combined with the term *"Lymphocytes, Tumor-Infiltrating"* [Mesh] and *"Immunotherapy, Adoptive"* [Mesh]*"* combined with the term "*Neoplasms*" [Mesh]*"*, using the Boolean operator *AND*. The terms were defined by the *Medical Subject Headings* (MESH). The filters used were: "*Free full text*"; "10 *years*"; "*Humans*" and "*Cancer*". All steps are demonstrated in Figure 1.

The material used for analysis were classic articles, clinical essay, systematic review, meta-analysis, and bibliographic review. The first exclusion criterion was the title adequacy to the analyzed topic. Then, another level of exclusion was executed after reading the abstracts of works that did not fit within the scope of the objective. Finally, among those that approached similar themes, the more recent articles were preferred over the less recent. The remaining articles were read in full and their content was described in the results according to the relevance of their contribution to the objective of this work.

Aiming to fully tend to the objective, 13 related articles were found on PubMed database through specific and individual researches during the writing phase of the project or were chosen among the references of articles that had been previously studied.



Source: Authors.

Figure 1 – Process of article selection flowchart

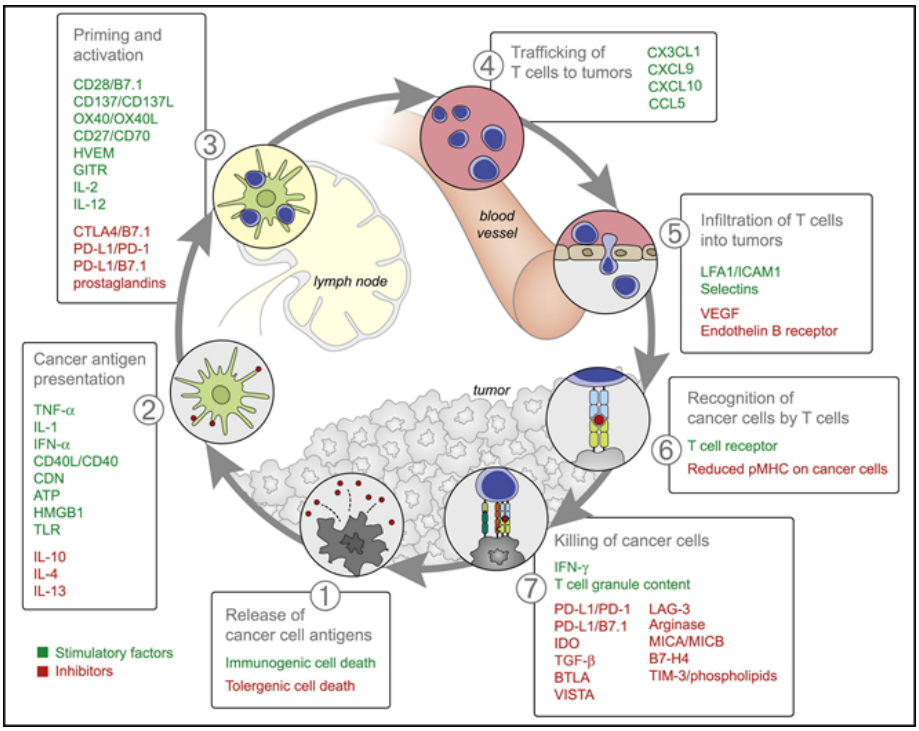
RESULTS

Cancer and immunologic system

The concept that the human body defense cells can recognize and control the growth of a tumor exists since 1891, when William Bradley Coley conceived the idea of eradicating his patients' tumors by stimulating an immune response capable of combating those cells. Coley then proposed that the immunologic reaction to controlled infections could also fight against the tumors present on his patients. To create these infections, *Streptococcus sp* were injected in his patients, later being followed by Coley's Toxins (toxins originated from the emulsion of bacteria)[3]. His work "*The treatment of malignant tumors by repeated inoculations of Erysipelas, with a report of ten original cases"*, published in 1893, is currently seen as an important milestone responsible for a new line of thought and research in the treatment of diseases such as cancer, for it demonstrates that the immune system may create a reductive effect on tumors or even make them disappear[4,5].

A series of gradual events, called the Cancer-Immunity Cycle (Figure 2), must occur for the immune response to happen. On the first stage, the neoantigens created by the oncogenesis are released and captured by the dendritic cells (DCs) for processing. There must be a production of stimulatory immunogenic signs, such as pro-inflammatory cytokines and factors released by tumor cells, so an anticancer T cell response can be created at this step.

Afterwards, the DCs present the antigens captured in the molecules of the main histocompatibility complex (MHC I and II) to the T cells, resulting in the activation of the effector T cells response against the cancer specific antigens, which are seen as foreign. The nature of the immune response is determined at this stage, based on a critical balance of the proportion between effector T cells *versus* regulatory T cells, that being the key for the outcome. Finally, the activated effector T cells transit and infiltrate in the tumor, recognizing and connecting to the carcinogenic cells through the interaction between its T Cell Receptor (TCR) and the antigen connected to the MHC I, promoting the death of the target carcinogenic cell. The release of the antigens resulting of this process will feed the first stage of the cycle, increasing the amplitude and depth of the immune response[6].



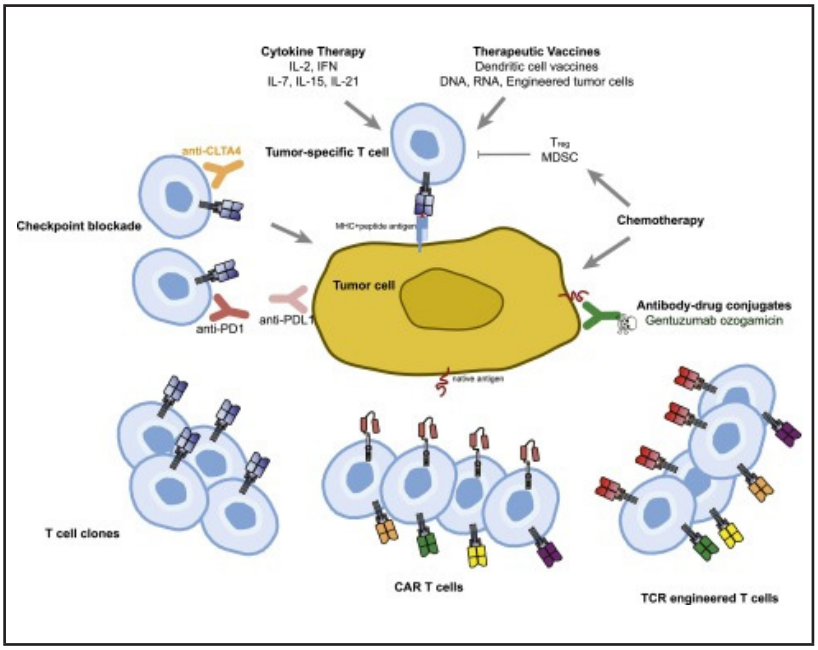
Source: Chen and Mellman[6].

Figure 2 – Cancer-immunity cycle highlighting the stimulating and inhibiting factors of each stage

In patients with cancer, the cycle of immunity against cancer does not have an ideal performance, which can be due to: tumor antigens may not be detected; DCs and T cells may treat antigens as autologous factors, instead of foreign, creating regulatory T cells response instead of effector T cells response; T cells may be inhibited from infiltrating the tumor; factors in the tumor microenvironment may suppress the production of effector cells[7].

Therefore, immunotherapy may create a self-sustained cycle of cancer immunity so it can amplify and propagate by itself, without generating rampant autoimmune inflammatory responses that may harm the cells and normal tissues.

Thus, different therapeutic approaches (Figure 3) have been developed and enhanced[8], such as checkpoint inhibitors, the transference of adoptive cells by creating expanded clones of cytotoxic T cells or T cells manipulated to express TCRs or CARs (chimeric antigen receptors), cytokines and vaccines. These techniques will be discussed below.



Fonte: Maus et al[8].

Figure 3 – Therapeutic approaches to cancer treatment

Checkpoint inhibitors

The blockage of the immune checkpoint was developed as a therapeutic treatment through understanding that the malign neoplasms may usurp the pathways of immunologic checkpoint, through agents such as the protein 4 associated to cytotoxic T lymphocytes (CTLA-4) and the PD-1 protein. This strategy has been shown to be effective in many solid tumors, such as melanoma, lung cancer, liver cells cancer and urothelial cancer[9].

Myeloid-derived suppressor cells (MDSCs) are important cellular components of the tumor microenvironment. The MDSCs act mainly to suppress the activity of immune cells. The chemokines produced by different tumors may actively recruit MDSCs to primary site tumors and metastatic tumors. The PD-L1 expression on the surface of the MDSCs that infiltrate the tumor suppress the T cells activity through the connection to PD-1[10].

The identification of PD-L1 as an immune modulator expressed in 20% to 50% of human cancers led to the development of several cancer immunotherapies that aim to interrupt the interactions between the tumor receptor and the stimulatory protein of the lymphocyte, such as PD-L1:PD-1, PD-L1:B7.1 and PD-L2:PD-1. The response rates in immunotherapy with anti-PD-L1 and anti-PD-1 antibodies were presented to more than 750 patients (varying from 13% to 38%) treated from an ample array of types of human cancers. Therefore, it is believed that for many human cancers, the cycle of cancer immunity is intact until the point of tumor cells death through T cells, that may be restricted potently by PD-L1. Once blocked the interaction PD-L1:PD-1, the preexistent anticarcinogenic T cells may have their effector function restored rapidly, allowing the secretion or production of the cytotoxic mediators that are necessary to kill the tumor cells[6].

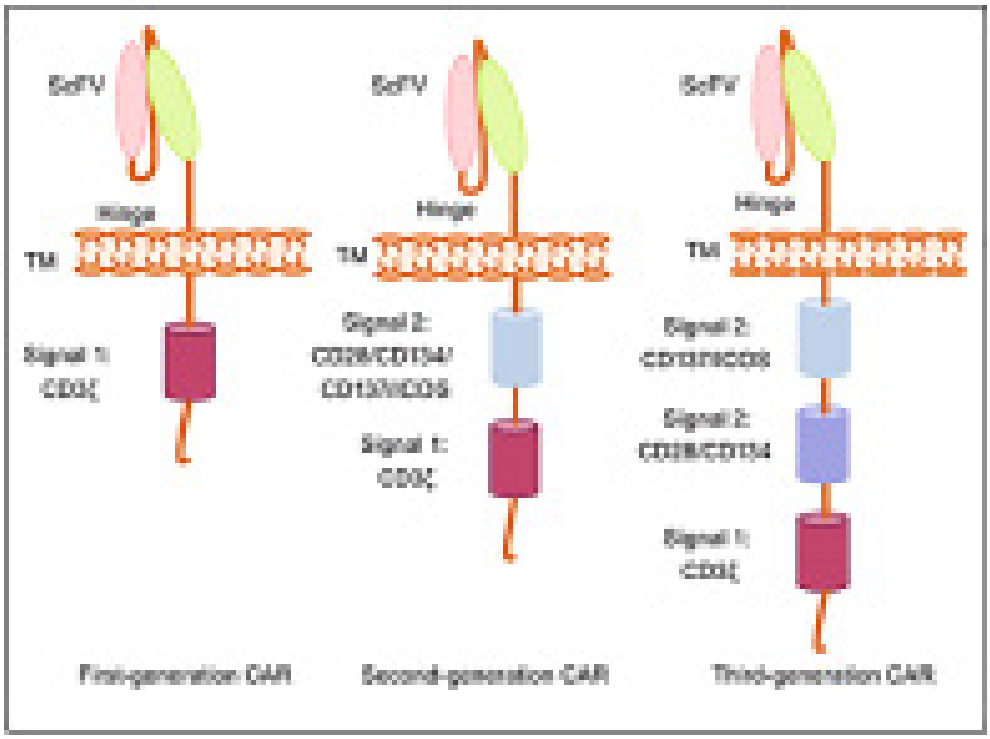
According to Zhang and Chen[11], more than 100 clinical trials are ongoing to test the efficacy and safety of immune checkpoint blockers in different types of cancer. Ipilimumab, for example, has been already approved by the Food and Drug Administration (FDA) as a treatment against melanoma and multiple cancers. The same is true for Nivolumab and Pembrolizumab, both targeting PD-1.

Adoptive cell therapy

T CAR cells

It is possible to observe that chimeric antigen receptor cells (T CAR) are currently the most precise tool in immunotherapeutic treatment. These cells consist of CD8 T lymphocytes extracted from the patients themselves during their immunotherapeutic treatment. After the extraction, the lymphocytes are kept in a growth medium where they are introduced to the specific tumor tissue antigens. The contact with these antigens, added to the refined biochemical stimuli, makes the chimeric cells genetically able to produce receptors in their membrane, designated as chimeric antigen receptors (CAR), which will be the antitumor response trigger. Thus, it is possible to affirm that the T CAR cell is produced artificially through genetic engineering, and the method of its application to the patient is known as adoptive T CAR cell transfer.

CAR are transmembrane proteins that consist in three main functional domains: (a) an extracellular antigen-recognition region which contains a single chain variable fragment (scFv); a plasmatic membrane hinge and (c) the intracellular activation, which had its structure modified with the advance of the studies in the area, allowing the differentiation between the three main generations (Figure 4).



Source: Li H and Zhao Y[12].

Figure 4 – CAR generations layout

The 1st generation cells were limited to signal 1 and didn't have costimulatory molecules able to maintain the immune response for more than a few weeks. Such obstacle was overcome by the 2nd generation molecules, which are constituted by costimulatory molecules responsible for keeping the cells activated, enabling effective antitumor responses, in addition to signal 1. The 3rd generation is characterized for having more than one costimulatory domain, but the results of the treatment do not show a significant improve from the 2nd generation, thus decreasing its usage[12].

The clinical application of T CAR cells therapy was described in the case report of a glioblastoma on the right temporal lobe of a 50-year-old man, which took place on the City of Hope Beckman Research Institute and Medical Center. Brown *et al.*[13] verified that intraventricular infusions present a better antitumor response in relation to the intracavitary infusions, demonstrating the relevance inherent to choosing the best method for T CAR cells application for maximum infiltration and activity in the tumor tissue. Moreover, the authors highlighted the presence of mild collateral effects, such as headaches, general fatigue, myalgia and olfactory auras; and the patient's returned to his labor activities, previously interrupted by conventional radiotherapy treatments[13].

It is worth emphasizing that the immunotherapy application in neurological cancers, such as glioma, represents hope for patients, since that diseases are

characterized for a high level of lethality. However, the treatment of cancers involving the central nervous system requires attention to elements such as: this tissue's low power of regeneration, its essential functionality and anatomical restrictions, such as the skull's inelasticity, which may aggravate situations of edema or inflammation induced by the immune cells.

Considering these elements, the choice of target antigens for the immunological effectors requires a rigorous study regarding the specificity of the target to minimize the chance of irreversible damage to the healthy tissue caused by antitumor cells[14].

MILs Cells

The adoptive cell therapy (ACT) with marrow-infiltrating lymphocytes (MILs) may provide a higher antitumor immunity in hematologic cancers, since they are obtained from the tumor microenvironment of the patients themselves.

The clinical essay of Noonan *et al*[2] describes the use of MILs in the treatment of Multiple Myeloma, malignancy that attacks the bone marrow. In this study, twenty-five patients with recently diagnosed disease or relapse had their MILs activated and expanded in "*ex vivo*". Afterwards, they were subject of myeloablative therapy and after three days they received the MILs infusions. The research results revealed that the treatment with MILs led to a higher specific immunity to the myeloma[2].

The data obtained in the study attest to the higher specificity towards the tumor shown by activated MILs, revealing its great differential when compared to the peripheral blood lymphocytes that, in general, are used for infusions. Therefore, the familiarity with the immunological environment where the tumor is, considering the MILs innate antigenic specificity to the marrow's cells, its ability to traffic more easily to the marrow after infusion and its persistence over time reiterate better efficacy of MILs when fighting the tumor[2].

Moreover, according to Baskar and Muthusamy[15], the hematologic malignancies are considerate particularly adequate to therapeutic interventions with immune responses mediated by cells or antibodies. Therefore, immunotherapy's applicability in hematologic cancers is seen as one of the most noticeable, especially considering adoptive cell therapy.

TIL Cells

The use of Tumor-Infiltrating Lymphocytes (TILs) indicate higher chances of satisfactory generation of antitumor response, since it has local action and familiarity with the immunologic environment of the treated tumor[16].

However, TIL cell intervention is still hardly feasible due to the constant need for specialized workforce for its production, creating high costs and a high abandon rate for patients during treatment, considering the delay in TILs production. TILs demand 5 to 6 weeks to be produced with a 60% to 90% success rate in cases of melanoma tumors[17]. On that account, a study by Besser et al.[18] aimed to observe the proceedings of a new TILs production technique which consisted on reducing the incubation period to make the process more accessible without losing efficacy, hence reducing the patient abandon rate. It was observed that with the transfer of Young-TIL, minimally incubated, to 20 patients, 10 presented an objective clinical response, including 2 fully complete responses and 8 partials, with only transient and manageable side effects[18].

Another challenge for TILs is the existence of metastatic melanoma patients with unresectable lesions, which makes it impossible for the extraction of infiltrating T lymphocytes to supply the therapy[19].

Natural Killer Cells (NK)

NK cells are the first line of defense against carcinogenic cells, they have the ability to identify and eliminate those cells rapidly, since they are capable of recognizing what belongs to the organism and what does not through the expression of killer inhibitory receptors. These receptors interact with markers (e.g. main histocompatibility complex class I) in healthy cells, and when the cells become stressed and lose those markers, the NK cells are activated[20]. When the high cytotoxicity generated by those cells is directed to the tumor cells, it enables the reduction of malignant tissue.

However, the NK cells are not found in significant numbers in advanced neoplasms. Therefore, restoring its antitumor functionality may be a promising therapeutic strategy. NK cells that are activated and expanded *ex vivo* may supplement dysfunctional NK cells. According to Levy et al.[21], immunotherapy based on cytokine-induced killer (CIK) cells became a promising new strategy. The CIK cells are a mix of T lymphocytes, expanded *ex vivo* with cytokines, comprehending CD3+/CD56+ cells, CD3+/CD56+ natural killer (NK) cells and CD3+/CD56+ cytotoxic T cells. These cells have a high proliferation rate, potent antitumor effects because of the functional capacity of both the T cells and the NK cells, plus low cytotoxicity for normal cells and substantial selectivity for tumor cells[22].

The safety and efficacy of dendritic cell (DC) immunotherapy and cytokine-induced killer (CIK) was evaluated on breast cancer by Hu et al.[23]. It was verified that DC/CIK therapy combined with chemotherapy increased significantly the antitumor response, although it has presented collateral effects, such as leukopenia, thrombocytopenia, hair loss, nausea, hepatic complications and neurological complications (which are typical of chemotherapy). However, the author report that the advantage of the new therapy over the conventional is the

preciseness on the combat against tumor cells, reducing the death of healthy cells. Furthermore, they also indicate a smaller development of drug-resistance, allowing the use of the therapy for a longer period, and stressed the importance of immune surveillance after the death of the tumor cells[23].

Cell vaccines

Tumor Cell Vaccines consist in injecting the patient with the attenuated tumor cells (either autologous or allogenic) that were genetically modified to stimulate the immune response. During preparation, its "camouflage" ability is removed, and the malignant cells can stimulate the synthesis of costimulatory molecules, cytokines or both combined. This new property enables the presentation of tumor antigens that initiate the immune response.

To reach a better performance, Antigen-Presenting Cells (APCs) are also stimulated through granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4 (cytokines) and CD80 (costimulatory molecule). Pre-clinical trials on mice with gliosarcoma demonstrated that IL-4 infusion is the one with the most therapeutic benefits, since it is responsible for producing an antitumor response based on activating T-Helper Lymphocytes. A therapeutic improve was also seen when Interferon type I was injected into the intracranial cavity[24].

Another important type is the dendritic cell vaccines. These cells are efficient in inducing and regulating immune responses. They can present tumor antigens in several forms. The vaccine may be manufactured through synthetic antigens production, similar to those of the tumor, or by isolating antigens from the tumor itself to enable the action of the dendritic cells. It is also possible to transfer messenger RNA that code these antigens to such cells, stimulating the synthesis of these substances, which initiate the immune response[25].

CONCLUSION

Immunotherapy is a field of cancer treatment in exponential development. The knowledge of the potential of the immune system against carcinogenic cells is not recent; however, the application of immunotherapeutic approaches gained strength recently. Studies are increasing in numbers to unveil and manipulate the immune mechanisms involved in the fight against this diseased, propelled by the advent of new technologies. Today, immunotherapy is already seen as one of the most remarkable treatments against hematologic cancers. Moreover, these therapies have gained ground on treating solid cancers.

The ascension of immunotherapy introduce an alternative for patients with cancer, for it may work around problems and limitations of conventional therapies. Some of its promising evidences is the attenuation of side effects because of the personalization of the immunotherapeutic strategy, preventing the destruction of non-tumor cells. It is also worth mentioning the gain in immune surveillance, in which the organism keeps monitoring and eliminating the tumor cells, and the smaller development of drug-resistance, which allows the prolongated use of the therapy.

It is also remarkable that immunotherapeutic approaches may be associated to conventional treatments, showing even more satisfactory results when compared to the application of immunotherapy only, such as in the treatment of metastatic melanoma and breast cancer.

Among the types of immunotherapy that were covered in this work, the checkpoint inhibitors are an alternative that is already available on the market. Many medicaments were approved by the FDA, consolidating this type of therapy as main treatment for melanoma and metastatic cancers, for example.

However, the most positive results have been with adoptive cell therapies, such as MILs, TILs and especially those that use T CAR cells. Clinical trials showed the innovative response of those cells against glioblastoma, a solid cancer that hitherto had not been combated by immunotherapeutic mechanisms. However, the mass application of these therapies is still a challenge, since the adoptive cell production still does not have consolidated methods of production and involves high-cost genetic engineering.

Although many immunotherapeutic approaches are experimental and their broad application still shows to be uncertain, the results obtained by clinical trials demonstrate an exciting perspective for this new horizon on the fight against cancer.

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