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REVIEW

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Chemotherapy: A partnership with immunotherapy in non-small cell lung cancer

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Abstract

Chemotherapy (CT) and immunotherapy (IO) act synergically in the treatment of non-small cell lung cancer (NSCLC). However, the molecular basis of such interaction is poorly understood. The aim of this review was to explore the mechanisms of CT to potentiate the immune system and, consequently, the action of IO. The most up-to-date knowledge concerning the interaction of CT and IO in NSCLC was reviewed and a bibliographic search was made in PubMed/Medline database, using the mentioned keywords, with preference given to recently published articles in English.

In addition to the direct cytotoxic effect, CT affects the immune system leading indirectly to cell death. The immune response triggered by PD-1 inhibition is enhanced by the cytotoxic immunogenic effects of CT. This potentiation phenomenon occurs due to an increase in effector cells relatively to regulatory cells, inhibition of myeloid derived suppressor cells, increased potential for cross-presentation by dendritic cells after the death of tumor cells or blocking the STAT6 pathway to increase dendritic cell activity.

In conclusion, the effects of CT on the immune system work in synergy with the actions of IO, transforming "cold" tumors into "hot" tumors, which are more visible to the immune system.

KEYWORDS

chemotherapy, immunotherapy, non-small cell lung cancer

INTRODUCTION

An immunosuppressive microenvironment is a hallmark of cancer and contributes to carcinogenesis. Antineoplastic therapeutic interventions aim to interrupt this inhibitory mechanism, increasing antitumor immunity.[1] In non-small cell lung cancer (NSCLC), immunotherapy (IO) drugs are approved, namely antiprogrammed death ligand 1 (PD-L1, atezolizumab), antiprogrammed death 1 (PD-1, pembrolizumab or nivolumab) or anti-CTLA-4 (ipilimumab). Recently, the use of IO has shown good results in adjuvant and neoadjuvant treatment, after or combined with chemotherapy (CT).[2–4] As for metastatic disease, in naïve patients, when there is an expression of the tumor protein PD-L1 equal or greater than 50%, in the absence of molecular targets, the first therapeutic option is pembrolizumab or atezolizumab in monotherapy.[5] However, tumors that express high levels of PD-L1 are a minority and other therapeutic strategies are needed.[6] CT acts on tumor cells through its direct destruction, interfering with deoxyribonucleic acid (DNA) synthesis and its replication, but also cooperates with the immune system for tumor elimination. In this review we explain the mechanisms through which CT enhances the effect of IO.

METHODS

An electronic search was carried out in PubMed/ Medline database. Original and review papers were included,

TABLE 1 Conventional antineoplastic drugs used in combination with pembrolizumab, atezolizumab and nivolumab plus ipilimumab, in patients with metastatic NSCLC

Class	Biochemical activity	Biological effects	Approved in combination with immunotherapy in NSCLC
Platinum compounds	Crosslinks DNA strands	Inhibition of DNA replication and transcription	Carboplatin Cisplatin
Taxanes	Stabilizes tubulin in microtubules	Inhibition of mitosis	Paclitaxel *Nab*-paclitaxel
Pemetrexed	Folate antimetabolites	Inhibition of purine and pyrimidine synthesis	Pemetrexed

Abbreviations: DNA, deoxyribonucleic acid; NSCLC, non-small cell lung cancer.

published between 2002 and 2022, written in English, with complete text available. The terms "chemotherapy," "immunotherapy," "non-small cell lung cancer," "immunotherapy combined with chemotherapy" were searched.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

The immune system is responsible for detecting and eliminate cancer cells. In order to grow, tumors create an immunosuppressive microenvironment by avoiding recognition by T cells, recruiting and retaining of regulatory T cells (Treg), secreting of immune-regulating and suppressive cytokines and mediators, and by downregulation of T cell checkpoint pathways.[7] Tumor associated macrophages (TAM) and tumor associated neutrophils (TAN) produce cytokines and create cellular interactions that block the immune response and promote cell proliferation.[8] In addition, tumor cells express PD-L1, a transmembrane protein, that link to the T lymphocyte PD-1 transmembrane protein, activating immunosuppression mechanisms.[9] Oncogene mutations interfere with IO treatment strategies and somatic mutations lead to the production of neoantigens recognized by the immune system, mediating tumor sensitivity to IO.[9–11]

Therefore, CT is used to potentiate the benefit of IO based on its off target cytotoxic effect. Table 1 presents antineoplastic drugs used in combination with IO.

For instance, paclitaxel induces mitotic catastrophe resulting from failed mitosis.[12] Additionally, CT induces cell death by acting as an immunomodulator, either through the immunosensitization of tumor cells, emitting specific signals that act as a trigger for phagocytosis, or by stimulation of macrophages, dendritic cells and natural killer cells (NK),[13] as described below.

Immunosensitization of tumor cells

CT induces an effective immune response through its action on tumor cells, triggering immune-mediated death. These mechanisms include increasing the expression of death receptors and inducing the release of cytochrome c by mitochondria.[14] Drugs like paclitaxel or cisplatin permeabilize tumor cells to granzyme B through upregulation of mannose-6-phosphate (M6P), a receptor on tumor surface.[15] Compounds derived from platinum stimulate the expression of natural killer group 2D (NKG2D) ligand, a NK-cell activating receptor, resulting in an increased NK-cell cytotoxicity and production of interferon-γ (IFN-γ).[16] Consequently, CT affects the phenotype of malignant cells that survive antineoplastic treatments, making them susceptible to immune-mediated lysis, synergizing with IO.[17]

Action on the immune system

Antineoplastic agents function as immunomodulators of the immune system. These drugs provoke cellular rearrangements, making the dying cells more noticeable to the immune system, induce a transient lymphodepletion, inhibiting the mechanisms of immunosuppression, and exert stimulatory effects on the effector immune cells.[18]

Therefore, the immune response caused by the inhibition of PD-1 is enhanced by the immunogenic effects of cytotoxic CT. This potentiation phenomenon happens due to an increase in effector T cells (Teff) in relation to regulatory T cells (Treg), inhibition of myeloid derived suppressor cells (MDSCs), increased potential for cross-presentation by dendritic cells after death of tumor cells, or blocking the STAT6 pathway to increase the activity of dendritic cells.[19]

Increased action of effector in relation to regulatory T cells

Dying cell components, resulting from CT action, are presented to the immune system to generate a specific humoral response, mediated by Teff.[20] To defend itself, the tumor microenvironment creates a defense mechanism that favors the proliferation of cancer cells, enriched with Treg with suppressive function. Treg cells have several mechanisms to inhibit Teff antitumor activity. Some studies suggest that enzymes such as arginase I, indoleamine 2,3-dioxegenase (IDO) and nitric oxide synthase (NOS), as well as some surface molecules, such as latency-associated peptide (LAP) and CD124, are related to immunosuppression and tumor progression.[21,22] Based on this mechanism, the cytotoxic effects of CT may play an important role in the destruction of these suppression mediators that create immune-

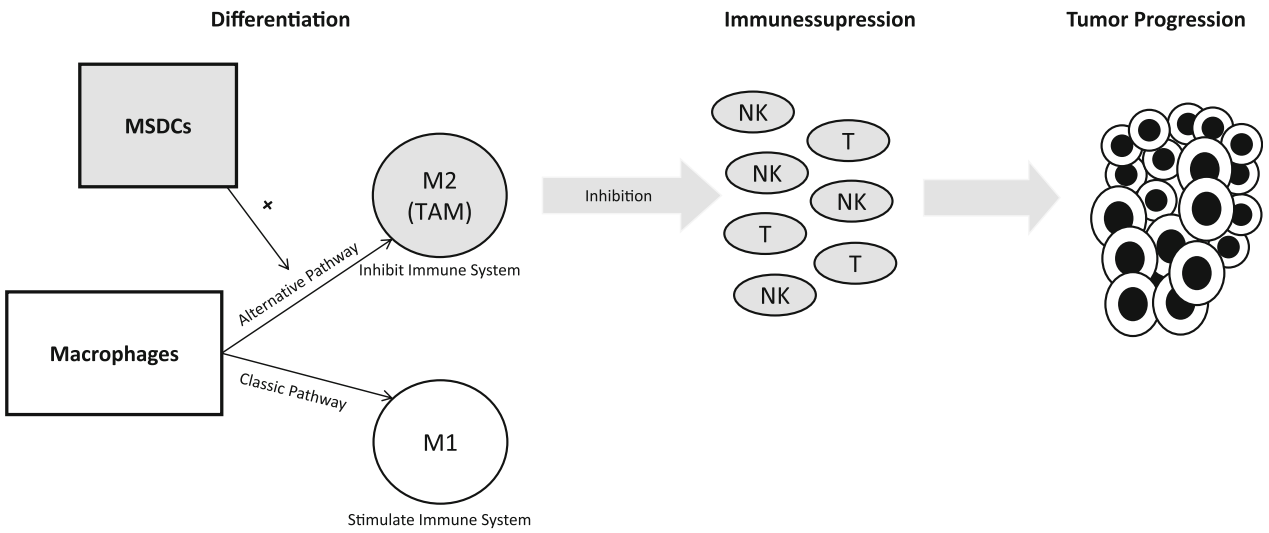

FIGURE 1 Macrophages differentiation pathways and respective effects.

mediated tumor tolerance. Sim et al. demonstrated that in blood samples from patients with advanced NSCLC, treated with platinum compounds, there was a decrease in the expression of IDO, NOS and CD124, showing the relevance of CT in the immune-mediated tumor combat.[23]

In other studies of patients with NSCLC, the combination of cisplatin and vinorelbine appeared to increase the ratio between Teff and Treg (Teff/Treg), by reducing the immunosuppressive activity of Treg in most patients. Roselli et al. documented a significant difference in the absolute number of Treg relatively to the abundance CD4 + T cells, in samples collected after the third cycle compared to the baseline.[24] Gameiro et al. showed that the Teff recovery time was shorter than that of the Treg, resulting in an increase in the ratio Teff/Treg.[25] It was also observed that proliferation of CD4 + T cells was mediated through stimulation with anti-CD3 antibodies, not affected by CT.[26]

Inhibition of suppressor cells derived from myeloid cells

MDSCs are a subset of immunosuppressive cells that accumulate both in peripheral lymphoid organs and at the tumor level.[26,27] For their development, tumors induce MDSCs that play an immunosuppressive role through several mechanisms, such as:

- Inhibiting the proliferation and activation of CD4+ and CD8+ lymphocytes through arginase-1, NOS or IDO.[23,28] On the other hand, MDSCs induce loss of expression of T cell ζ-chain receptor and desensitization of this receptor through the production of reactive oxygen and nitrogen species;[29]
- Activation of macrophages. Macrophages differentiate, through monocytes, into classically activated macrophages (M1) or alternatively activated macrophages (M2), having effective and suppressive functions, respectively. MSDCs lead to the activation of macrophages by the alternative route, forming M2, with a consequent increase in the formation of IL-10.[30] TAMs share many characteristics with M2, having a pro-oncogenic function through immunosuppressive effects on NK and T cells, favoring tumor progression[31] (Figure 1). In this setting, paclitaxel, for instance, directly stimulate the cytotoxicity on TAMs and induce the activation of tumor-specific dendritic cells, NK and T, through the secretion of IL-12 and TNF-α;[32,33]
- Inhibiting cytotoxicity, NKG2D expression and the production of IFN-γ by NK cells, through a cell-contact-dependent mechanism that involves the membrane-bound transforming growth factor β (TGF-β);[34]
- Inducing immunosuppressive Treg and promote the upregulation of PD-L1 via hypoxia-inducible factor-1α (HIF-1α);[39 35]
- Leading to tumor growth, by a nonimmunomediated process, inducing neovascularization, epithelial-mesenchymal transition and increasing stemless of cancer cells.[36–39]

CT has been shown to reduce MDSCs, both at the tumor level and in peripheral lymphoid organs. Inhibition of accumulation of MDSCs with various antitumor therapies appear to be dose- and time-dependent.[26] Paclitaxel, in animal models, at a dose of 1 mg/kg, has been found to cause a significant reduction in MDSCs in tumors and restores CD8 + T cells with effector function. At clinical level, the 175 mg/m^2 dose demonstrated a modest increase in the absolute number and percentage of circulating MDSCs. Therefore, the exclusive use of paclitaxel may result in different numbers of circulating MDSCs, depending on the administered dose. It has also been shown that the effect was not the same for all locations, since low doses of paclitaxel cause a significant reduction in primary tumor MDSCs, but not in metastatic ganglia, spleen or bone marrow.[40]

Increased potential for cross-presentation by dendritic cells after tumor cell death

CT has direct immunostimulatory effects on dendritic cells by enhancing their maturation and function. Tanaka et al. revealed that cisplatin and paclitaxel have an impact on the maturation mechanisms of dendritic cells, their growth and survival. However, some antineoplastic drugs, which stimulate the release of signals for cell maturation, have a direct cytotoxic effect superior to the effect obtained on cell maturation, causing the death of dendritic cells. This group includes topoisomerase inhibitors, antimicrotubule agents and two alkylating agents (mecloretamine and diaziquone).[41]

For instance, dendritic cells exposed to carboplatin during their maturation induced a significantly greater proliferation of T cells compared to other CT agents, producing higher levels of IFN-γ and IL-2 compared to those activated by unexposed dendritic cells. Platinum-derived compounds also reduce the expression of inhibitory molecules, such as PD-L1 and programmed death ligand 2 (PD-L2), both in tumor cells and in dendritic cells. PD-L2 in particular is profoundly reduced by the STAT6 pathway through its dephosphorylation (inactivation), resulting in increased proliferation of specific antigens and secretion of Th1 cytokines, as well as increased recognition of tumor cells by T cells.[14,42,43]

This double action of increasing the immunostimulatory potential of dendritic cells and decreasing the immunosuppressive capacity make platinum-compounds a good option for combination with IO over paclitaxel, as the latter has direct cytotoxic effect on dendritic cells, possibly causing their death.[1]

Implications in the conjugation of CT with IO

Antineoplastic agents that stimulate cell death through immunostimulation convert the tumor into an endogenous vaccine, a phenomenon that occurs by the stimulation of dendritic cells, being ideal candidates for combination with IO to eliminate immune suppressor cells, as demonstrated in NSCLC.[44] Furthermore, the inhibition of immunosuppression by CT creates a favorable opportunity for combination with IO, with an increase of the reactive immune response to the tumor. The time of administration between CT and IO also have implications and, to achieve the maximum synergism of both treatments, IO should immediately follow CT (1–2 days apart).[45]

CONCLUSIONS

CT promotes rearrangements of tumor cells for presentation, making them more noticeable to the immune system. In addition, they influence the homeostasis of the hematopoietic component through transient lymphodepletion followed by refilling by pools of immune cells. The subversion of suppressor mechanisms induced by the tumor and the increase in stimulatory effects, direct or indirect, of immune effectors also enhance tumor suppression via the immune system. These mechanisms work in synergy with IO, turning "cold" tumors into "hot" tumors, which are more visible to the immune system.

AUTHOR CONTRIBUTIONS

Conception or design of the work: Ana Sofia Mendes. Data collection: Ana Sofia Mendes and Raquel Romão. Data analysis and interpretation: Ana Sofia Mendes and Raquel Romão. Drafting the article: Ana Sofia Mendes. Critical revision of the article: All Authors. Final approval of the version to be published: All Authors.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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