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Commentary

Conditioning neoadjuvant therapies for improved immunotherapy of cancer

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ABSTRACT

Recent advances in the treatment of melanoma and non-small cell lung cancer (NSCLC) by combining conventional therapies with anti-PD1/PD-L1 immunotherapies, have renewed interests in immunotherapy of cancer. The emerging concept of conventional cancer therapies combined with immunotherapy differs from the classical concept in that it is not simply taking advantage of their additive anti-tumor effects, but it is to use certain therapeutic regimens to condition the tumor microenvironment for optimal response to immunotherapy. To this end, low dose immunogenic chemotherapies, epigenetic modulators and inhibitors of cell cycle progression are potential candidates for rendering tumors highly responsive to immunotherapy. Next generation immunotherapeutics are therefore predicted to be highly effective against cancer, when they are used following appropriate immune modulatory compounds or targeted delivery of tumor cell cycle inhibitors using nanotechnology.

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1. Introduction

Combinatorial cancer therapies such as chemo-immunotherapy, radio-immunotherapy, or targeted therapies combined with immunotherapy have been rationally designed to impinge on different pathways of tumor growth in order to achieve additive or synergistic anti-tumor effects. For instance, patients with HER2/neu overexpressing breast cancer receive chemotherapy and anti-HER2/neu antibody therapy using Trastuzumab and Pertuzumab. Chemotherapeutics such as doxorubicin increase free radicals that cause DNA damage, as well as intercalate into DNA and disrupt the DNA repairing function of topoisomerase-II [1]. Trastuzumab induces antibody dependent cellular cytotoxicity (ADCC), increases endocytotic destruction of the receptor, and inhibits shedding of the extracellular domain of HER2/neu [2] while Pertuzumab inhibits homo- and hetero-dimerization of HER2/neu, thereby blocking signalling pathways of tumor cell proliferation [3]. The caveat for such traditional chemo-immunotherapies is that standard dose chemotherapies are highly toxic to the host immune system and thus less effective for being simultaneously combined with immunotherapy (Table 1). Recent advances in our understanding of the mechanisms of action of low dose versus high dose chemotherapies are changing the concept of and approaches to chemo-immunotherapeutic design. Many studies demonstrated that certain chemotherapeutics at low doses induce immunogenic tumor cell death (ICD) and confer immune stimulatory effects. Therefore, the rationale for low dose chemotherapies is to condition tumor cells to become highly responsive to immunotherapies. A similar concept applies to the combined use of other cancer therapies, particularly those that induce cell cycle arrest, as conditioning regimens for an effective immunotherapy of cancer. The new chemo-immunotherapeutic approaches are predicted to make immunotherapies highly effective against cancer (Table 1).

2. Low dose metronomic (LDM) chemotherapy for an effective immunotherapy of cancer

Standard chemotherapy dosing regimens have traditionally used the maximum tolerated dose (MTD) of a drug administered with acceptable side effects as determined through clinical trials. In addition to targeting the malignant cells, the nonspecific cytotoxic drugs damage healthy cells with a high proliferation rate such as gastrointestinal mucosal and immune cells. Consequently, an extended time period is required between treatments in order to allow for tissue recovery. LDM chemotherapy is an alternative dosing regimen that is characterized by administering a cytotoxic drug at a low dose scheduled at a regular interval in order to minimize the drug-free time periods. Metronomic dosing schedules aim to achieve adequate disease control with less toxicity than MTD chemotherapy. The rationale for LDM is to not only inhibit tumor growth but also induce ICD and anti-tumor immune responses [4–7] to make patients highly responsive to immunotherapies. A LDM chemotherapy can control tumor progression in patients with early stage as well as those with advanced-stage cancers [8].

2.1. Non-immunogenic mechanisms of LDM chemotherapy

Proliferating malignant cells' oxygen requirements are met by forming inappropriate vascularization to the tumor. Tumor hypoxia results in the production and release of angiogenic cytokines, which leads to resistance to both antiangiogenic and chemotherapeutic regimens [9,10]. One of the earliest studies using low dose chemotherapy at regular intervals referred to the dosing regimen as antiangiogenic scheduling [11]. The study found that low dose cyclophosphamide given at regular schedule was able to kill cells that were resistant to a standard dose chemotherapy. The results have been reproducible [12,13], though the efficacy of low dose chemotherapy as a first line treatment for untreated cancers is yet to be determined. The tumor regression was attributed to sustained endothelial cell apoptosis that occurred due to the higher frequency dosing, which did not occur during the drug-free periods used in MTD chemotherapy. In fact, circulating endothelial cells are released from the bone marrow as an adaptive response to marrow suppression induced by MTD chemotherapy, allowing for damaged tumor cells to regenerate. In this aspect LDM chemotherapy has a unique mechanism in suppressing vasculogenesis by suppressing the source of vascular growth factors [14]. Promotion and maintenance of angiogenesis involves a balance of proangiogenic and antiangiogenic molecules acting within the tumor microenvironment. One of the earliest growth factors released from the tumor site in response to hypoxia is the transcriptional regulator, HIF-1alpha. Doxorubicin at a LDM regimen has been reported to block this transcription factor, the inhibition of which has been shown to overcome resistance to antiangiogenic therapies and promote tumor regression [15,16]. LDM chemotherapy has been shown to decrease expression of proangiogenic molecules VEGF and VEGF receptor 2 [17] and increase the expression of the antiangiogenic thrombospondin 1 [18]. Taken together these data indicate that LDM chemotherapies suppress the tumor microenvironment's response to hypoxia by suppressing angiogenesis.

2.2. Immunogenic mechanisms of LDM chemotherapy

Certain chemotherapies at the MTD have been associated with immune stimulation through the induction of ICD. The term ICD was first introduced over a decade ago by Dr. Kroemer's group to indicate a functionally peculiar type of cell death induced by certain chemotherapeutics that can elicit an immune response against damage associated molecular patterns (DAMPs) in the absence of any adjuvant [19]. Inducers of ICD include doxorubicin, cyclophosphamide, epirubicin, idarubicin, mitoxantrone, bleomycin, bortezomib, 5-fluorouracil, paclitaxel and oxaliplatin [20,21]. On the other hand, some other chemotherapeutics such as cisplatin fail to induce ICD [22]. Animals challenged with doxorubicin-sensitized tumor cells were able to mount anti-tumor immune responses that protected them from re-challenge with tumor cells of the same type [19]. Recent studies demonstrated that the lack of ICD is correlated with poor prognosis for breast cancer patients

Table 1
Current concepts on combinatorial cancer immunotherapies.

Concept	Objective	Approach	Weakness	Strength
Traditional	To impinge on different pathways of tumor growth in order to achieve additive or synergistic anti-tumor effects	Adjuvant therapies at maximum tolerated doses	Toxicity Immune suppression	Tackle multiple drug resistant mechanisms
New	To condition the tumor microenvironment and make tumor cells highly responsive to immunotherapy	Low dose neoadjuvant conventional therapies and standard dose adjuvant immunotherapy	Tumor immunoediting and escape	Immune stimulatory Safe

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