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Commentary

Combining antibody–drug conjugates and immune-mediated cancer therapy: What to expect?

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ABSTRACT

Blockade of immune-checkpoints has emerged as one of the most promising approaches to improve the durability of anti-tumor responses in cancer patients. However, the fraction of patients experiencing durable responses to single agent immune checkpoint inhibitor treatment remains limited. Recent clinical reports suggest that patients responding best to checkpoint blockade therapies display higher levels of $CD8^+$ T-cells in the tumor prior to treatment. Therefore, combination treatments of immune-checkpoint inhibitors with compounds that increase the number of tumor infiltrating $CD8^+$ T cells may expand the therapeutic benefit of immuno-oncology (IO) drugs.

Immunogenic cell death (ICD) of tumor cells is induced by certain classes of cytotoxic compounds and represents a potent stimulator of effector T-cell recruitment to tumors. In addition, several cytotoxics directly stimulate dendritic cell activation and maturation, resulting in improved anti-tumor immune responses when combined with IO compounds. Among them, several cytotoxic agents are currently utilized as payloads for antibody–drug conjugates (ADCs). Therefore, identification of optimal combination regimens between ADC- and IO compounds holds strong promise to overcome the current limitations of immune checkpoint inhibitors, by increasing the recruitment of $CD8^+$ effector T-cells to the tumor core.

Here we review the emerging field of ADC/IO combination research, with a focus on how to optimally combine both modalities. The answer to this question may have a broader impact on oncology drug development, as synergistic activities between IO compounds and ADCs may increase the formation of tumor specific immunological memory, ultimately leading to durable responses in a larger fraction of cancer patients.

1. Introduction

During the past two decades of preclinical and clinical research, much progress was made towards the improvement of both safety and efficacy of ADCs. In particular, the development of site-specific conjugation technologies [1–5], combined with improvements in linker chemistries [6], enabled higher ADC exposure levels, thereby overcoming the dose limiting off-target toxicities of conventional ADCs, while maintaining anti-tumor efficacy. In addition, a plethora of payloads with different mechanisms of anticancer activity have been developed for application in the ADC context. These new linker-payloads now provide a unique opportunity of matching the mechanism of ADC pharmacology with tumor biology and cancer indications.

Simultaneously with the development of these "next generation ADCs", a paradigm shift in oncology drug development occurred, with immuno-oncology drugs becoming increasingly prominent due to their enhancement in the durability of anti-tumor responses. Recent treatment successes with antibodies that regulate immune activation such as CTLA-4 [7] and PD-1 [8] improved the fraction of patients with complete and partial responses relative to standard of care (SOC) treatment (reviewed in Ref. [9]). The first approval by the U.S. Food and Drug Administration (FDA) of an immune checkpoint inhibitor targeting CTLA-4 (ipilimumab) for the treatment of advanced melanoma occurred in 2013 [10], coincident with the approval of the first ADC targeting solid tumor indications, T-DM1 in Her2 positive breast cancer (reviewed in Ref. [11]). Subsequently, clinical trials with blocking antibodies targeting the immune checkpoint mediator

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programmed cell death 1 (PD-1) and its ligand (PD-L1) have resulted in objective and durable responses in cancer patients with treatment-refractory solid tumors, including melanoma and cancers of the lung and kidney [12,13].

The key differentiating attributes of IO compounds are the increased recognition of tumor antigens by $CD8^+$ T-cells and induction of tumor-specific immunological memory in cancer patients. These attributes are considered the biological drivers behind the long lasting responses seen in subsets of patients treated with IO compounds, frequently manifested during early treatment cycles. Given these clinical successes, cancer immunotherapy is likely to become a key part of the clinical management of cancers. Despite these early clinical successes, only a subset of cancer patients responds to single agent immunotherapies, and combination treatments with other immune checkpoint inhibitors or different therapeutic modalities are needed to increase the fraction of patients benefitting from IO treatment [14]. As a consequence, combination studies with IO compounds have become a central focus of the current preclinical- and clinical development activities in oncology. Better understanding of the molecular and cellular mechanisms limiting the anti-tumor activities of current IO compounds is critical to inform the selection of optimal combination treatment regimens between IO compounds and other anti-cancer therapeutics for clinical development in oncology.

In response to antineoplastic agents, the composition of the tumor immune infiltrates can be predictive for outcomes of therapy. An increased number of $CD3^+$ T-lymphocytes as well as an increased ratio of cytotoxic $CD8^+$ T-lymphocytes (CTLs) over $FOXP3^+$ regulatory T-cells (Tregs) within tumors following chemotherapy treatment was predictive of favorable therapeutic responses in human breast and colorectal cancer patients treated with anthracyclines and oxaliplatin, respectively [15–17]. Therefore, combination treatments of IO compounds and SOC regimens, in tumor indications showing responses to single agent IO compounds including melanomas, lung and renal cancers, represents an attractive clinical development strategy (reviewed in Refs. [18,19]). However, there are several concerns when combining IOs with certain SOCs including chemotherapy. One being the notion that the dose-limiting toxicities of SOC cytotoxic regimens, in particular lymphopenia and neutropenia, may interfere negatively with the mechanism of action of IO compounds, and to impair clonal expansion of effector lymphocytes and/or disturb the homeostasis of immune cells [20]. In support of these concerns, meta-analysis of multiple clinical trials indicated that severe lymphopenia ($<$1000 lymphocytes/μL) correlates negatively with the response to chemotherapy in multiple solid tumor indications [21]. The drop in peripheral lymphocytes induced by many standard chemotherapeutic regimens may thus limit the response to IO compounds, as the activities of the latter depend on the presence of tumor infiltrating leukocytes (TILs, reviewed in Ref. [19]). Additionally, the tumor microenvironment has been shown to actively impede effector cell functions, thereby limiting the efficacy of TILs activated and recruited to tumors by immune-based therapies [22]. A potential way to circumvent such negative interference between cytotoxic and IO compounds is by staging the two modalities, and by providing sufficient time after cytotoxic treatment for the lymphoid cell population to recover prior to initiating IO treatment. In support of this concept, combination of SOC chemotherapeutics with IO compounds administered concomitantly failed to improve clinical outcome. In contrast, when chemotherapy was given prior to IO treatment (sequentially), an increase in progression free survival was observed [23,24].

An alternative way to address the concerns of negative interference between IO and cytotoxic compounds is to employ targeted chemotherapeutics, in particular next generation site-specific ADCs, which induce less off-target toxicities by preventing the premature release of payloads [1,3,6]. The following chapter will briefly summarize the progress made in the emerging field of ADC/IO combination research. In particular, we review two distinct mechanisms of action of cytotoxic agents, each involving different target cell populations within tumors.

2. The role of ADCs in the cancer immunity cycle: direct activation and maturation of dendritic cells by tubulin inhibitors

One mechanism by which cytotoxic compounds induce anti-tumor immunity is via direct activation and maturation of dendritic cells (DCs). The second mechanism is tumor cell intrinsic and is known as immunogenic cell death (ICD), preceding tumor cell death (reviewed in next section). Importantly, both mechanisms have been shown to engage the adaptive immune response through improved cross presentation of tumor derived antigens and priming of specific $CD8^+$ effector T-cells, thereby triggering an immune response towards the tumor (Fig. 1). Given the potential of both mechanisms to address some of the current limitations of single agent IO treatments, combination of IO compounds with ADCs represent a promising area of future ADC research, both preclinically and clinically.

Therapeutic induction of tumor-cell apoptosis combined with DC activation and maturation by select SOC chemotherapies, represents an attractive combination approach for IO compounds (reviewed in Ref. [25]). Due to their highly sophisticated antigen-presenting machinery, DCs are central to the initiation and regulation of anti-cancer immunity [26]. However, tumors have evolved several mechanisms to interfere with the maturation and antigen processing capacity of tumor residing DCs [27–29]. In contrast to mature DCs, which efficiently promote tumor immune responses, immature or dysfunctional DCs can induce immunosuppressive effects. Tumors exploit these properties by suppressing DC maturation or inducing a dysfunctional state, allowing tumors to avoid immune recognition (reviewed in Refs. [30,31]). Therefore, therapeutic approaches that activate tumor resident DCs and promote the priming of tumor antigen-specific T cells may address the limitations of current anti-cancer therapeutics and increase cancer immunity. However, only a few studies have investigated the capacity of cytotoxic cancer therapeutics, as employed by ADCs, to improve DC functions.

One of the earliest reports identifying cytotoxic compounds with immune stimulatory functions triggering immune surveillance included the mitotic spindle inhibitor vinblastine, targeting the beta subunit of tubulin. Vinblastine was identified as a potent and direct inducer of DC maturation, which is different from its antimitotic activities on tumor cells [32–34]. In an extension of this work, a large variety of tubulin poisons were shown to induce DC activation and maturation, when exposed to mouse or human dendritic cells, indicative of a class effect. When tested in vitro, colchicine, vinblastine, vindesine, vincristine, combretastatin-A4, dolastatin 10, dolastatin 15, monomethylauristatin E (MMAE), ansamitocin P3 and DM1 induced phenotypic and functional dendritic cell (DC) maturation and activation [35]. The experimental endpoints used to study DC activation and maturation included expression of the co-stimulatory molecules and the maturation marker CD80 and CD86 and production of the pro-inflammatory cytokines IL-1β, IL-6 and IL-12. Additional studies testing dolastatin 10 and the synthetic analog MMAE as well as the maytansinoid, ansamitocin P3 [36,37], were conducted in preclinical tumor growth experiments in mice. These three cytotoxics are commonly used as payloads for ADCs and stimulated $CD8^+$ effector cell migration to experimental tumors grown in mice. When tested