



Does ipilimumab show an increased clinical benefit when combined in sequence with chemotherapy?

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Ipilimumab is a fully human monoclonal antibody against cytotoxic T-cell lymphocyte antigen-4 (CTLA-4), which is not expressed by resting T cells and is only detected in activated T cells (1). CTLA-4 is known as a crucial negative regulator of the immune system, as it binds to B7 ligands (CD80/CD86) on antigen-presenting cells (APCs) with a high affinity and competes with costimulatory receptor CD28 on T cells for binding with B7 ligands (2). Ipilimumab works by blocking the binding of CTLA-4 to its ligands and augments T cell activation, leading to tumor regression (3). In contrast to conventional T (Tconv) cells, regulatory T (Treg) cells, which suppress aberrant immune responses, including the anti-tumor immune response, constitutively express CTLA-4 (4). Therefore, ipilimumab evokes effective tumor immunity by killing effector Treg cells or attenuating their suppressive activity.

In phase 3 trials, ipilimumab improved the overall survival (OS) in patients with advanced melanoma (5). The common adverse events (AEs) were pruritus, rash, and diarrhea. Grade 3 or 4 immune-related AEs (irAEs) occurred in 10% to 15% of patients and were managed using drug-specific treatment guidelines, such as the administration of corticosteroids. Intriguingly, the administration of the chemotherapeutic agent dacarbazine plus ipilimumab also improved the OS in patients with previously untreated metastatic melanoma compared with dacarbazine plus a placebo [11.2 *vs.* 9.1 months, respectively; hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.59–0.87; $P < 0.001$] (6). However, grade 3 or 4 AEs occurred in 56.3% of patients treated with dacarbazine plus ipilimumab, compared with 27.5% of patients treated with dacarbazine plus a placebo. Furthermore, grade 3 or 4 irAEs occurred more frequently

in the dacarbazine plus ipilimumab group (41.7%) than in the dacarbazine plus placebo group (6.0%) but were also managed using well-established guidelines. These findings urged oncologists to perform clinical trials of chemotherapy plus ipilimumab in several cancers.

However, in the current phase 3 study of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer (NSCLC), this regimen did not improve the OS compared with placebo combined with paclitaxel and carboplatin (13.4 *vs.* 12.4 months, respectively. HR, 0.91; 95% CI, 0.77–1.07; $P = 0.25$) (7). Grade 3 or 4 treatment-related AEs (TRAEs) occurred in 51% of patients treated with chemotherapy plus ipilimumab, compared with 35% of patients treated with chemotherapy plus placebo. The rate of discontinuation due to TRAEs was higher with chemotherapy plus ipilimumab (28%) than with chemotherapy plus placebo (7%). However, despite these discouraging findings, we still believe that there is something fascinating about the combination regimen of chemotherapy plus ipilimumab. Resourceful efforts, such as those described below, are needed to make the most out of this regimen.

We herein review the current knowledge on the synergy between ipilimumab and chemotherapy.

Rationale for the combination of ipilimumab with chemotherapy

Based on several findings, the following rationale for the combination of chemotherapy and ipilimumab is conceivable: (I) chemotherapy leads to tumor cell death and the release of

tumor-specific antigens known as neoantigens, which initiate the activation of T cells and move them into tumor tissues (8); (II) chemotherapy enhances tumor cells' susceptibility to T cell-mediated killing in preclinical models (9); (III) chemotherapy prolonged the antitumor effects via the induction of a memory immune response when combined with ipilimumab in animal models of several tumors (10); (IV) chemotherapy induced the release of neoantigens from dying cells, which in turn recruited and activated Treg cells in tumor tissues. Ipilimumab exerts antibody-dependent cytotoxicity against Treg cells in tissues (4).

Neoantigens

Neoantigens are not generally recognized by the host immune system, so no tolerance is induced. In contrast, chemotherapy induces the release of neoantigens from dying tumor cells. Neoantigens then induce T cell proliferation and increase the population of antigen-specific T cells in the draining lymph nodes (11). In addition, signals from chemotherapy or dying tumor cells regulate the antigen uptake, antigen processing, and presentation, thereby inducing dendritic cell (DC) maturation, co-stimulation, polarization, and trafficking (12).

Tumor permeability

Cytotoxic T cells exert their cytotoxic effects through the Fas/FasL and perforin/GrzB pathways. Although chemotherapy does not affect the expression of Fas/FasL, it increases the permeability of tumor cells for GrzB and makes tumor cells more sensitive to cytotoxic T cells. This effect is mediated by the upregulation of mannose-6-phosphate receptors on tumor cells both in mice and humans. As a result, chemotherapy enhances the antigen recognition of T cells and is able to induce apoptosis in neighboring tumor cells, even if they do not express their antigen (9).

Memory immune response

The combination of ipilimumab and chemotherapy shows a synergistic and durable anti-tumor effect in several cancer models, including lung cancer (10). Intriguingly, in these models, most mice treated with a combination of ipilimumab and chemotherapy rejected the tumor re-challenge. This memory immune reaction rarely happened in mice treated with chemotherapy alone, suggesting that the combination of chemotherapy plus ipilimumab resulted in a protective memory immune response.

Treg cells

Although ipilimumab was first suggested to augment the activity of tumor-infiltrating T cells, recent studies have shown that ipilimumab also affects Treg cells, thereby enhancing the anti-cancer immune response (4). Tumor killing by chemotherapy releases neoantigens, and these recruits and activates Treg cells in tumor tissues, which suppresses any aberrant immune response to neoantigens. Therefore, to activate the effector T cells, Treg cells must be depleted and their suppressive activity attenuated by cancer immunotherapy targeting Treg cells. Ipilimumab exerts a Treg-depleting effect by targeting effector Treg cells, which are abundant in tumor tissues and express high levels of CTLA-4 (4). Taken together, these findings suggest that the sequence of chemo-immunotherapy is quite important for effective cancer treatment.

Consideration of the sequence of the administration of chemotherapy and ipilimumab

Although, chemotherapy induces immune responses by generating neoantigens from dying cells in preclinical models, such chemotherapy generally suppresses the immune system in humans during a standard regimen (9). In addition, the concurrent combination of immune checkpoint inhibitors causes more discontinuation due to severe AEs than monotherapy (13). Therefore, the sequence of the administration of chemotherapy and immunotherapy is considered to be vital to improve the OS (11).

Preclinical studies have shown the enhancement of the anti-cancer effect by administering immunotherapy after chemotherapy (14). Indeed, a phase II study in which patients with chemotherapy naïve NSCLC were randomly assigned 1:1:1 to receive paclitaxel and carboplatin with either placebo, concurrent ipilimumab (four doses of ipilimumab plus chemotherapy followed by two doses of placebo plus chemotherapy), or phased ipilimumab (two doses of placebo plus chemotherapy followed by four doses of ipilimumab plus chemotherapy), demonstrated the feasibility and better outcomes of a phased schedule of chemotherapy and ipilimumab than a concurrent schedule (15). However, in the current phase 3 study, the phased schedule of ipilimumab combined with chemotherapy did not improve the OS in patients with advanced squamous NSCLC (7). One reason is that the toxicity and higher discontinuation rate in the chemotherapy plus phased ipilimumab group reduced the

chemotherapy exposure. In fact, only 52% of patients in the chemotherapy plus phased ipilimumab group received the 4 planned therapy sessions, compared with 76% of patients in the chemotherapy with placebo group (7). However, the 2-year OS rates of 5 mg/kg of nivolumab, a programmed death-1 (PD-1) inhibitor, combined with concurrent chemotherapy reached 62% with relatively low discontinuation due to TRAEs (29%) (16). This discrepancy is due in part to the stronger toxicity or weaker anti-tumor effect of ipilimumab than nivolumab (13).

To take full advantage of ipilimumab combined in sequence with chemotherapy without exacerbating the AEs, we need to carefully determine the potential sequenced regimens in which chemotherapy is used first and followed by switching to ipilimumab only after progression occurs or later in a pre-defined course.

Patient selection based on novel biomarker identification

In the current phase 3 study of patients with advanced squamous NSCLC, two Kaplan-Meier survival curves cross between the phased ipilimumab combined with chemotherapy and placebo combined with chemotherapy regimens (7), suggesting that a strong predictive biomarker may help select the most-sensitive patients from a population, similar to the epidermal growth factor receptor (EGFR) mutation in the Iressa Pan-Asia Study (IPASS) (17). Many projects are searching for predictive biomarkers of an immunotherapy response and toxicity; however, the complexity of the immune mechanism has made this difficult. Several predictive biomarkers have been proposed, including an increased number of peripheral CD8 effector-memory type 1 (EM1) T cells or CD4⁺ICOS⁺T cells. In addition, antibodies against NY-ESO-1 detected pre- or post-treatment were correlated with a favorable clinical outcome (18-20). A flow cytometry analysis showed that low numbers of circulating Ki67⁺EOMES⁺CD8⁺ T cells and circulating CD45RO⁺CD8⁺ memory T cells were associated with a poor prognosis (21-22). The baseline circulating levels of TGF- β 1 and IL-10 were associated with relapse following ipilimumab therapy (23).

However, while these may be useful predictive markers, laborious procedures make them hard to use routinely. In contrast, baseline and post-treatment changes in leucocyte counts and levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) may be candidates for predictive markers for a response, as these data are routinely available (23). Intriguingly, Sade-Feldman *et al.*

demonstrated that circulating CD33⁺CD11b⁺HLA-DR⁻ myeloid-derived suppressor cells were useful as biomarkers for monitoring the immune status of patients (24). However, while this will surely facilitate the appropriate selection of patients fit to continue chemo-immunotherapy, their study had a small sample size and lacked a validation cohort.

Conclusions

Chemo-immunotherapy appears to have a number of challenges yet to overcome. Future data from preliminary clinical studies will help us administer this therapy most effectively to achieve the best patient outcomes. Although the ideal sequence, schedule, and combination of the potential effects of chemo-immunotherapy with the best risk-benefit profile as well as predictive biomarkers remain unknown, chemo-immunotherapy is an evolving treatment modality that can provide a long-term survival across a broad range of tumors.

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