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Publication Date

2022-08-01

DOI

10.1016/j.pharmthera.2022.108111

Peer reviewed



HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Pharmacol Ther. 2022 August ; 236: 108111. doi:10.1016/j.pharmthera.2022.108111.

The Immune Modifying Effects of Chemotherapy and Advances in Chemo-Immunotherapy

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Abstract

Immune checkpoint inhibitors (ICIs) have transformed the treatment paradigm for several malignancies. While the use of single-agent or combined ICIs has achieved acceptable disease control rates in a variety of solid tumors, such approaches have yet to show substantial therapeutic efficacy in select difficult-to-treat cancer types. Recently, select chemotherapy regimens are emerging as extensive modifiers of the tumor microenvironment, leading to the reprogramming of local immune responses. Accordingly, data is now emerging to suggest that certain anti-neoplastic agents modulate various immune cell processes, most notably the cross-presentation of tumor antigens, leukocyte trafficking, and cytokine biosynthesis. As such, the combination of ICIs and cytotoxic chemotherapy are beginning to show promise in many cancers that have long been considered poorly responsive to ICI-based immunotherapy. Here, we discuss past and present attempts to advance chemo-immunotherapy in these difficult-to-treat cancer histologies, mechanisms through which select chemotherapies modify tumor immunogenicity, as well as important considerations when designing such approaches to maximize efficacy and improve therapeutic response rates.

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AUTHOR CONTRIBUTIONS

DP drafted the manuscript and assembled figures/tables. SK, MK, and HM critically edited the manuscript.

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Conflict of Interest Disclosure: The authors have no conflicts to disclose.

DECLARATION OF COMPETING INTEREST

The authors have no conflicts to disclose.

Keywords

Cancer; chemotherapy; immunology; immune checkpoint inhibitors; tumor microenvironment

1 – INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy in the last decade and are now the preferred first-line treatment for several solid cancers. ICI-based immunotherapy consists of neutralizing antibodies against surface proteins that serve to negatively regulate immune function, most notably cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-1 ligand 1 (PD-L1), thus impeding the ability of tumor cells to evade the cytotoxic immune program (Wei, Duffy, & Allison, 2018). These approaches have demonstrated substantial anti-tumor activity in most cancers (Borghaei, et al., 2015; Darvin, Toor, Sasidharan Nair, & Elkord, 2018; Garon, et al., 2015; Gibney, Weiner, & Atkins, 2016; Hodi, et al., 2010; Larkin, et al., 2015; Robert, et al., 2011), and have largely replaced chemotherapy as the preferred treatment for select cancers including melanoma, renal cell carcinoma, and others (Robert, 2020). However, despite significant advances in cancer immunotherapy, there are several cancer types in which ICIs have yet to show significant single-agent efficacy. Additionally, the development of ICI-refractory disease remains a pressing issue in clinical oncology, as many patients initially able to achieve adequate disease control with ICI-based immunotherapy may eventually progress on treatment and require additional line therapy (Barrueto, et al., 2020).

Contrasting the long-held belief that chemotherapy is immunosuppressive, mounting evidence suggests several cytotoxic chemotherapy regimens have various immunostimulatory effects, leading to extensive reprogramming of the tumor immune microenvironment and potentiating therapeutic responses to immunotherapy (Bracci, Schiavoni, Sistigu, & Belardelli, 2014; Emens, 2008; Opzoomer, Sosnowska, Anstee, Spicer, & Arnold, 2019; Wargo, Reuben, Cooper, Oh, & Sullivan, 2015). Accordingly, several chemo-immunotherapy regimens have now been approved by the FDA, with others showing early promise in clinical trials. In this review, we discuss past and present advances in chemo-immunotherapy, with a particular emphasis on difficult-to-treat cancer histologies. Additionally, we describe the many mechanisms through which chemotherapy can modify the tumor immune microenvironment and how this can be utilized in novel combinations to maximize treatment efficacy and improve therapeutic response rates for cancers in which ICIs have yet to show significant benefit.

2 – EARLY RATIONALE FOR COMBINING CHEMOTHERAPY AND IMMUNOTHERAPY

The intersection between chemotherapy and immunotherapy has long been under clinical evaluation. Though initial reports showed no added benefit to combining Bacille Calmette-Guérin (BCG) and broad-spectrum chemotherapy (Jacquillat, Banzet, & Maral, 1982), several subsequent trials sought to exploit preclinical observations that select chemotherapy

agents can deplete what would come to be known as regulatory T-lymphocytes (Tregs), thereby promoting local immune responses. Tregs comprise a specialized T-cell subpopulation that acts to inhibit sterilizing immune responses and promote peripheral tolerance (Kondelkova, et al., 2010), and several have hypothesized that a reduction in tumor-associated Tregs may augment responses to cancer immunotherapy. Much of the early research on chemotherapy-induced Treg-depletion focused on cyclophosphamide, an alkylating agent belonging to the nitrogen mustard family (Ahmed & Hombal, 1984; Hughes, et al., 2018).

Tregs are highly sensitive to cyclophosphamide, particularly when compared to cytotoxic T lymphocytes (CTLs) and helper T cells (Heylmann, et al., 2013). Thus, cyclophosphamide has long been suggested as a potential means of targeting Tregs to potentiate cancer immunotherapy (Figure 1). This concept has been under investigation for nearly 40 years, following the 1982 observation that cyclophosphamide enhances the efficacy of adoptive transfer in the Meth A fibrosarcoma mouse model (North, 1982). More recent studies have confirmed that cyclophosphamide-mediated Treg depletion can enhance the efficacy of immunotherapy in a rat model of implanted PROb colon cancer cells (Ghiringhelli, et al., 2004), potentiate non-myeloablative allogeneic stem cell transplantation through increased activation of autoreactive T-cells (Takeuchi, et al., 2012), and increase the frequency of active T-cell infiltration in tumor-bearing mice (P. Liu, Jaffar, Hellstrom, & Hellstrom, 2010).

Though these and several other studies support cyclophosphamide as an immune modifier, translating these findings to clinical practice has been difficult. Very early reports indicated that treatment with cyclophosphamide can enhance the development of delayed-type hypersensitivity responses in otherwise unreactive patients with metastatic colorectal cancer or melanoma (Berd, Mastrangelo, Engstrom, Paul, & Maguire, 1982). Subsequent studies suggested that cyclophosphamide can enhance local immune cues and/or deplete suppressive CD4 responses (Berd, Maguire, & Mastrangelo, 1984a, 1984b; Berd & Mastrangelo, 1987, 1988). This led to trials using cyclophosphamide as an adjuvant to therapeutic vaccines, first in melanoma. In a 1986 trial, pre-treatment with cyclophosphamide followed by an autologous melanoma cell vaccine led to objective clinical responses in only 2/19 patients (Berd, Maguire, & Mastrangelo, 1986), despite observations that cyclophosphamide can impede suppressor cell responses (Hoon, Foshag, Nizze, Bohman, & Morton, 1990). Similarly, cyclophosphamide failed to meaningfully enhance immune responses to a melanoma antigen vaccine, inducing delayed-type hypersensitivity responses in 15/18 patients compared to the 16/22 receiving only the vaccine, with no difference in overall or disease-free survival between groups (Oratz, et al., 1991).

Subsequent trials have also shown mixed results. A larger trial of 64 melanoma patients reported that the combination of cyclophosphamide and a therapeutic vaccine led to clinical responses in 5/40 evaluable patients with a median duration of 10 months (Berd, Maguire, McCue, & Mastrangelo, 1990). In a cohort of 121 patients with stage III melanoma, adjuvant cyclophosphamide and vaccination with either a GM2 ganglioside or GM2 ganglioside plus BCG showed poor efficacy, failing to show a statistically significant improvement in disease-free or overall survival (Livingston, et al., 1994).

Cyclophosphamide was next combined with a therapeutic lyophilized melanoma vaccine and interferon α (IFN α), and of the 39 evaluable patients, 10.2% showed a response with a median time to progression of 8 months (Vaishampayan, Abrams, Darrah, Jones, & Mitchell, 2002). Subsequent trials have explored cyclophosphamide in combination with several other immunotherapies, though overall therapeutic efficacy has been relatively modest (Alexandru, Van Horn, & Bota, 2010; Audia, et al., 2007; Dudley, et al., 2005; Dudley, et al., 2008; Emens, et al., 2009; Ghiringhelli, et al., 2007; Holtl, et al., 2005; Ladoire, et al., 2010; Laheru, et al., 2008; Nistico, et al., 2009). Hence, while cyclophosphamide is still being evaluated in combination with newer immunotherapy approaches, research has primarily shifted to explore the immunomodulatory effects of several other chemotherapy agents, as discussed in detail below.

3 – CHEMOTHERAPY-INDUCED ANTIGEN PRESENTATION

As ICIs have become a cornerstone of cancer therapy, there is an ever-growing interest in identifying new ways to predict treatment responses. Recent evidence suggests that select cancers with a high tumor mutational burden (TMB-H) are likely to be sensitive to ICIs, particularly when PD-L1 positive (Chan, et al., 2019). Similarly, several tumors deficient in DNA mismatch repair (dMMR) with high microsatellite instability (MSI-H) are sensitive to anti-PD-1 therapy (Le, et al., 2017), leading to the tissue-agnostic FDA approval of the anti-PD-1 antibody Pembrolizumab for MSI-H/dMMR solid tumors in 2017. The sensitivity of MSI-H/dMMR tumors to ICIs is primarily due to the presumptive increase in mutational burden, leading to a high prevalence of abnormal peptides (Le, et al., 2017). These endogenous proteins can be subjected to proteasomal degradation into peptides, some of which can be further trimmed by cytosolic proteases. These peptides then translocate to the endoplasmic reticulum (ER) via Transporters associated with Antigen Processing (TAP). They can undergo additional processing by ER Aminopeptidase (ERAP), as either free peptides or after being loaded onto a class I Human Leukocyte Antigen (HLA-I) molecule (Major Histocompatibility Complex or MHC in mice). In brief, once loaded onto an HLA-I molecule, a complex consisting of the HLA-I heavy chain, a β 2-microglobulin (β 2m), and the antigenic peptide is exported to the cell surface where it is presented for recognition by primed CD8+ CTLs (Jhunjhunwala, Hammer, & Delamarre, 2021).

However, for the majority of tumors that are not MSI-H/dMMR, diminished antigen presentation can be a significant barrier to the therapeutic efficacy of ICI-based immunotherapy, particularly for those with a low mutational burden such as pancreatic ductal adenocarcinoma (PDAC) (Principe, Korc, Kamath, Munshi, & Rana, 2021). Several reports suggest that chemotherapy can enhance the antigen presentation capacity of tumor cells, as discussed below. This potentially allows for more efficient priming of CD8+ CTLs and improving therapeutic responses to ICI-based immunotherapy, particularly for poorly immunogenic cancers (Figure 2).

3.1 – Platinum-based Chemotherapy

Platinum-based chemotherapy such as cisplatin, carboplatin, and oxaliplatin are widely used to treat several cancers. These drugs exert their cytotoxic effects mainly by interacting with

select guanine moieties of DNA, resulting in intrastrand crosslinks (Di Francesco, Ruggiero, & Riccardi, 2002), impeding strand replication and transcription (Woynarowski, Chapman, Napier, Herzig, & Juniewicz, 1998). However, in addition to their tumoricidal activity, these medications have extensive and well-studied effects on local immune responses, many of which can enhance antigen availability within the tumor microenvironment (TME) (Table 1) (Rebe, Demontoux, Pilot, & Ghiringhelli, 2019).

The immuno-stimulatory effects of cisplatin are perhaps the best-studied among the platinum-based antineoplastics, directing various immune cell processes, including antigen presentation (de Biasi, Villena-Vargas, & Adusumilli, 2014). This increase in antigen presentation has been suggested as a potential means through which cisplatin can potentiate anti-tumor immune responses alone or when combined with immunotherapy (Spanos, et al., 2009; Tseng, et al., 2008). For example, early reports demonstrate that cisplatin enhances tumor expression of MHC class I in colon cancer cells, exceeding that induced by non-platinum chemotherapy agents 5-fluorouracil (5-FU) or the irinotecan metabolite SN-38 *in vivo* (Ohtsukasa, Okabe, Yamashita, Iwai, & Sugihara, 2003). Similarly, in BALB/c mice inoculated with MOPC 104E plasmacytoma cells, cisplatin enhanced anti-tumor immune responses, increasing the expression of MHC class I antigens, but not that of MHC class II antigens (Nio, et al., 2000).

In patients with esophageal squamous cell carcinoma, the combination of neoadjuvant cisplatin and 5-FU led to a substantial increase in tumor-infiltrating CD4+ and CD8+ T-cells, as well as an increase in HLA-I expression when compared to chemo-naïve patients (Tsuchikawa, et al., 2012). In lung cancer cells, sublethal exposure to cisplatin and vinorelbine enhanced sensitivity to HLA-restricted cell death induced by CTLs, consistent with the enhanced presentation of tumor antigen (Gameiro, Caballero, & Hodge, 2012). Cisplatin also enhanced MHC class I expression in breast cancer cells (Wan, et al., 2012) and broadened the range of tumor antigens presented to CD8+ CTLs in a model of murine mesothelioma, suggesting that cisplatin reveals weaker tumor antigens to the cytotoxic arm of the immune system and may cooperate with cancer immunotherapy (Jackaman, Majewski, Fox, Nowak, & Nelson, 2012). This hypothesis is supported by recent preclinical observations in head and neck squamous cell carcinoma (HNSCC), where cisplatin enhanced antigen presentation and T-cell killing *in vitro* and cooperated with anti-PD-L1/PD-1 *in vivo* (Tran, et al., 2017).

Oxaliplatin also appears to have immunomodulatory effects in tumor cells, increasing antigenicity and promoting adaptive immune responses (W. M. Liu, Fowler, Smith, & Dalglish, 2010). Cisplatin and oxaliplatin have been suggested to induce similar immune alterations, also in preclinical models of HNSCC. Specifically, both increased surface expression of MHC class I and enhanced therapeutic responses to anti-PD-1 *in vivo* (S. J. Park, et al., 2019). In colon cancer cells, oxaliplatin resistance led to the differential expression of telomerase reverse transcriptase (TERT), cytochrome C oxidase assembly factor 1 (COA-1), and mesothelin tumor antigens, leading to tumor-cell targeting by antigen-specific CD4+ T-cells (Galaine, et al., 2019). This appears to be relevant clinically as high-risk rectal patients undergoing neoadjuvant oxaliplatin-based chemotherapy demonstrated systemic immune responses associated with improved overall survival (Kalanxhi, et al.,

2018). Similarly, in patients with metastatic hepatocellular carcinoma (HCC), neoadjuvant oxaliplatin-based chemotherapy enhanced both HLA-I and PD-L1 expression in tumors lacking an oncogenic RAS mutation, and the degree of immune response was associated with improved survival (Ledys, et al., 2018).

A recent study has offered a potential mechanism for oxaliplatin-induced antigen presentation. The lysine acetyltransferases p300/CREB-binding protein (CBP) appear to control the expression of MHC class I, as well as direct antigen processing/presentation, thereby controlling the abundance of neoantigen in tumor cells. The authors further demonstrated that, through an NF- κ B-dependent mechanism, oxaliplatin enhanced p300-mediated upregulation of MHC class I proteins, independent of IFN γ . Thus, oxaliplatin may enhance antigen presentation by overcoming epigenetic downregulation of MHC class I (Y. Zhou, et al., 2021).

Carboplatin may also enhance antigen presentation, though this is less established than with other platinum-based chemotherapies. Carboplatin appears to have immunogenic properties (Braly, et al., 2009) and increases HLA-I expression in ovarian cancer cells (Alagkiozidis, et al., 2011). However, in carboplatin-resistant ovarian cancer patients, increased HLA-I expression is associated with improved overall survival (Shehata, et al., 2009). Hence, the immunostimulatory effects of carboplatin warrant continued exploration, particularly in light of observations for structurally and functionally similar medications.

Beyond modulating antigen processing and presentation, platinum-based chemotherapy can also mobilize tumor-antigen by inducing immunogenic cell death (Figure 3). This process leads to increased damage-associated molecular patterns (DAMPs) within the TME, increasing the availability of tumor-antigen to professional antigen-presenting cells (APCs), thereby enhancing T-cell activation (Galluzzi, Buque, Kepp, Zitvogel, & Kroemer, 2017; Zhou, et al., 2019). The mechanisms through which cells undergo immunogenic cell death are diverse and highly complicated and have been linked to any number of cellular events, including exposure of calreticulin and other endoplasmic reticulum chaperones on the cell surface, autophagy and subsequent ATP release, Toll-like receptor 3 (TLR3) activation, as well as several cytokines and immune modulators including interleukin-1 β (IL-1 β), type I interferon (IFN), and CXCL10 (Galluzzi, et al., 2017; Zhou, et al., 2019).

In a seminal 2010 study, both oxaliplatin and cisplatin were shown to trigger the release of high-mobility group box 1 protein (HMGB1), an obligate step for immunogenic cell death (Tesniere, et al., 2010). However, only oxaliplatin stimulated the pre-apoptotic release of calreticulin. As both steps are required for immunogenic cell death, they determined that oxaliplatin was a more potent inducer of immunogenic cell death than cisplatin. In subcutaneous xenograft experiments, oxaliplatin-treated tumor cells induced a functional anti-cancer immune response that was mitigated by the silencing of calreticulin or HMGB1. Conversely, cisplatin failed to promote an anti-tumor immune response *in vivo* unless cells were supplemented with calreticulin. The authors further demonstrate that oxaliplatin-induced immunogenic cell death requires the HMGB1 receptor Toll-like receptor 4 (TLR4). Patients with a loss-of-function mutation to TLR4 display poorer progression-free and overall survival when treated with oxaliplatin-based chemotherapy (Tesniere, et

al., 2010). In a subsequent study from this group, the authors expanded on the failure of cisplatin to induce immunogenic cell death, which they attributed to an inability to activate protein kinase-like ER kinase (PERK)-dependent phosphorylation of eukaryotic translation initiation factor 2 α (eIF2 α). Cisplatin similarly failed to stimulate the formation of stress granules and macroautophagy, though this was reversed by the addition of ER stress-inducers thapsigargin or tunicamycin (I. Martins, et al., 2011). Hence, this approach warrants continued exploration.

While the ability of cisplatin to induce immunogenic cell death is still emerging, oxaliplatin is a well-established and robust inducer of immunogenic cell death, the degree of which is closely linked to its therapeutic efficacy (Tesniere, et al., 2010). In addition to triggering calreticulin and HMGB1, oxaliplatin-induced immunogenic cell death also involves several other mechanisms, including autophagy. Autophagy is dispensable for chemotherapy-induced cell death but is required for chemotherapy-induced trafficking of T-lymphocytes and dendritic cells (Michaud, et al., 2011). Knockdown of autophagy-related genes severely impairs pre-apoptotic secretion of ATP by tumor cells undergoing immunogenic cell death, and only autophagy-proficient tumor cells can induce anti-cancer immune responses *in vivo* (I. Martins, et al., 2012). Consistent with these observations, while autophagy-deficient tumor cells exposed calreticulin, released HMGB1, and underwent apoptosis in response to oxaliplatin, they secreted less ATP than autophagy-proficient controls. As autophagic cell death is often disabled in tumor cells, this may impair chemotherapy-induced cell death, including that induced by oxaliplatin, and strategies to compensate for this diminished ATP release warrant additional exploration (Michaud, et al., 2011).

3.2 – Non-Platinum-based Chemotherapy

Though platinum-based agents are perhaps the best-studied regarding chemotherapy-induced antigen presentation, several non-platinum medications have also been implicated in regulating the cross-presentation of tumor antigen (Table 2) and immunogenic cell death. For example, there is mounting evidence that the nucleoside analog gemcitabine (2', 2'-difluoro 2' deoxycytidine or dFdC) has several effects on tumor cell antigenicity (Gravett, Trautwein, Stevanovic, Dalglish, & Copier, 2018). Gemcitabine has been shown to enhance HLA-I expression in lung, breast, and colon cancer cells *in vitro*, as well as subcutaneous xenografts of colon cancer cells *in vivo* (W. M. Liu, et al., 2010). The effect of gemcitabine on HLA-I expression surpassed that of other medications in most cell lines, including cyclophosphamide and oxaliplatin (W. M. Liu, et al., 2010). Similarly, in B16 melanoma tumors, gemcitabine improved the cross-presentation efficiency of nuclear antigen in a dose-dependent manner (Anyaeibu, Lake, Heel, Robinson, & Fisher, 2014). The effects of gemcitabine on HLA-I have been confirmed in a similar study that determined that gemcitabine also altered the peptides eluted from HLA-I molecules (Gravett, et al., 2018). Though *in vivo* studies exploring are more limited, gemcitabine has also been shown to enhance HLA-I in various PDAC cell lines, and both xenograft and transgenic models of PDAC display enhanced MHC Class 1 expression following long-term treatment with gemcitabine (Principe, et al., 2020). Recent evidence suggests that gemcitabine treatment is also associated with a decrease in TAP, suggesting that gemcitabine may induce TAP-independent peptide loading of HLA-I (D. Li, et al., 2021). Accordingly, gemcitabine has

been shown to overcome poorly immunogenic phenotypes and cooperate with immune checkpoint inhibition *in vivo* (Principe, et al., 2020; Salewski, et al., 2021).

Several other drugs also appear to enhance antigen presentation and HLA expression. These include but are not limited to the topoisomerase I inhibitor topotecan, which enhanced HLA-I expression in breast cancer cells (Wan, et al., 2012). Similar results were observed using the non-platinum agents etoposide, paclitaxel, and vinblastine (Wan, et al., 2012). Additionally, the topoisomerase inhibitor mitoxantrone was reported to enhance p300-mediated upregulation of MHC class I, independent of autocrine IFN γ signaling (Y. Zhou, et al., 2021). In pancreatic cancer cells, several non-platinum medications have been shown to enhance surface expression of HLA-I, including paclitaxel, 5-FU, irinotecan, some surpassing that induced by oxaliplatin (Principe, et al., 2020). Hence, while data regarding non-platinum-based agents and HLA-I are still emerging, several widely used medications may similarly enhance antigen presentation and warrant continued exploration.

Finally, a variety of non-platinum chemotherapies promote immunogenic cell death. Gemcitabine can lead to immunogenic cell death, increasing the exposure of calreticulin and HMGB1 in lung cancer cells (Zhang, et al., 2020). For example, mitoxantrone, as well as the related medication doxorubicin, have also been linked to immunogenic cell death (Casares, et al., 2005; Obeid, et al., 2007), which is not observed using other topoisomerase inhibitors including camptothecin and etoposide (Sukkurwala, et al., 2014). Similarly, several studies demonstrate that bortezomib, a selective inhibitor of the 26S proteasome, can also induce immunogenic cell death, in part via activation of the cyclic GMP-AMP Synthase (cGAS)/Stimulator of Interferon Genes (STING) pathway (Gulla, et al., 2021; Serrano-Del Valle, Anel, Naval, & Marzo, 2019; Spisek, et al., 2007). Pemetrexed, a folate pathway inhibitor widely used in lung cancer, also induces immunogenic cell death, augmenting systemic intratumor immune responses and cooperating with cancer immunotherapy (Lu, et al., 2020; Schaer, et al., 2019). Accordingly, these and other medications have been suggested as a potential means of overcoming poor antigenicity and restoring functional anti-tumor immune responses (Casares, et al., 2005; Dudek, Garg, Krysko, De Ruyscher, & Agostinis, 2013; Schaer, et al., 2019).

3.3 – Chemotherapy and Dendritic Cell-Mediated Antigen Presentation

Though most studies have focused on chemotherapy-induced antigen presentation by tumor cells, additional evidence supports a role for chemotherapy in modulating the antigen function of professional antigen-presenting cells, mainly dendritic cells (DCs). Several chemotherapy agents have been shown to improve DC function at low doses, including cyclophosphamide, doxorubicin, methotrexate, mitomycin-C, paclitaxel, vinblastine, and vincristine (Kaneno, Shurin, Tourkova, & Shurin, 2009; Shurin, Tourkova, Kaneno, & Shurin, 2009). Several studies have offered mechanistic insight into the effects of chemotherapy on DC biology. For example, paclitaxel can directly affect DC maturation (John, et al., 2010; Pfannenstiel, Lam, Emens, Jaffee, & Armstrong, 2010). Further, paclitaxel has lipopolysaccharide-mimetic activity in mice, leading to the activation of TLR4 and enhancing DC activation and cytokine biosynthesis (Byrd-Leifer, Block, Takeda, Akira, & Ding, 2001; Kawasaki, et al., 2000).

Cyclophosphamide can increase circulating DCs during the recovery phase of drug-induced lymphodepletion, inducing their Flt3 ligand-dependent proliferation in the bone marrow prior to their expansion in the periphery (Salem, et al., 2010). These cyclophosphamide-induced DCs appear to have normal phagocytosis and antigen-presenting capacity (Salem, et al., 2009), though cyclophosphamide can enhance anti-tumor immunity by preferentially depleting CD8+ T-cell-resident DCs, leading to diminished Treg suppression and increased effector T-cell function (Nakahara, et al., 2010).

Several other drugs can alter DC biology. Conditioned media from gemcitabine-treated PDAC cells stimulates DC maturation, thereby potentiating tumor-specific cytotoxic T-cell responses (Pei, et al., 2014). Accordingly, gemcitabine treatment increases both monocytes and dendritic cells in patients with advanced PDAC (Soeda, et al., 2009), and gemcitabine has been successfully combined with a DC-based vaccine in murine PDAC (Bauer, et al., 2007). Additional evidence suggests that 5-FU and oxaliplatin decrease DC expression of immune checkpoints PD-L1 and PD-L2, promote DC maturation, and cooperate with therapeutic vaccination in tumor-bearing mice (X. Hong, et al., 2018). However, oxaliplatin can also promote PD-L1 expression on DCs and reduce the expression of the co-stimulatory molecules CD80/CD86, thereby decreasing T-cell responses (Tel, et al., 2012). Thus, the effects of these and other medications on DC function are likely complex, and additional factors, including drug dosing and duration, should be considered.

4 – CHEMOTHERAPY-INDUCED EXPRESSION OF IMMUNE CHECKPOINTS

Though chemotherapy has been shown to modulate immune-stimulating processes such as antigen presentation, several chemotherapy agents can also enhance the expression of immune checkpoints, with most focusing on PD-L1 (Figure 4). For example, in addition to enhancing immunogenic cell death and HLA-I, both cisplatin and oxaliplatin enhance surface expression of PD-L1 in HNSCC cells (S. J. Park, et al., 2019). Accordingly, cisplatin enhances therapeutic responses to PD-1/PD-L1 inhibition in a syngeneic mouse model of HNSCC (Tran, et al., 2017). In esophageal squamous cell carcinoma (ESCC) cells, incubation with carboplatin and paclitaxel or 5-FU and cisplatin enhanced PD-L1 expression in an Epidermal Growth Factor Receptor (EGFR)/Extracellular signal-regulated kinase (ERK)-dependent mechanism (Ng, et al., 2018). This relationship has also been evaluated in colorectal cancer, where neoadjuvant, oxaliplatin-based chemotherapy enhanced tumor PD-L1 expression only for patients without an activating RAS mutation (Ledys, et al., 2018). In TNBC cells, carboplatin, doxorubicin, gemcitabine, and paclitaxel have all been shown to enhance PD-L1 expression (Samanta, et al., 2018).

In NSCLC, patients receiving platinum-based neoadjuvant chemotherapy similarly displayed increased PD-L1 expression (Guo, et al., 2019; Shin, et al., 2019). In breast cancer cells, several drugs, including doxorubicin, paclitaxel, and topotecan, increase PD-L1 expression, which the authors presumed was due to a cell-stress response (Gilad, et al., 2019). In ovarian cancer, cisplatin paradoxically enhances antigen presentation and immunogenic cell death, as well as increases the surface expression of PD-L1 (Grabosch, et al., 2019). In PDAC,

several chemotherapy agents have been shown to enhance tumor expression of PD-L1, and in some cases, PD-L1 and CTLA-4. These include gemcitabine, paclitaxel, 5-FU, irinotecan, and oxaliplatin (Principe, et al., 2020). Gemcitabine-induced PD-L1 expression is further enhanced by the addition of a transforming growth factor β (TGF β) inhibitor (D. Li, et al., 2021), consistent with prior observations that tumors with systemic ablation of TGF β signals display increased PD-L1 expression (Principe, et al., 2019). Similar results have been reported in esophageal cancer in patients receiving neoadjuvant 5-FU and cisplatin, with enhanced PD-L1 expression localized to tumor-infiltrating immune cells (Fukuoka, et al., 2019). Though not an exhaustive summary, these and other related studies continue to provide evidence of chemotherapy-induced upregulation of immune checkpoints; the appropriately matched combination strategies warrant continued investigation (Bailly, Thuru, & Quesnel, 2020).

5 – CHEMOTHERAPY-INDUCED ALTERATIONS IN CYTOKINE SYNTHESIS

Chemotherapy has several, often contradictory roles in directing the local cytokine milieu, enhancing the biosynthesis of both immune-stimulatory and immune-suppressive signaling molecules (Figure 5). Early clinical observations noted that serum levels of the cytokines Granulocyte colony-stimulating factor (G-CSF) and IL-6 fluctuated in response to chemotherapy (Y. M. Chen, et al., 1996). Similar results have been observed *in vitro*, where etoposide and mitomycin C enhanced the production of several inflammatory cytokines, notably CXCL8 and Tumor Necrosis Factor α (TNF α) (Darst, et al., 2004). A seminal report in melanoma demonstrated that dacarbazine, temozolomide, and cisplatin enhance the release of various T-cell-attracting chemokines *in vitro*. This included several CXCR3 ligands as well as CCL5, which cooperated to attract tumor-infiltrating effector T-cells (M. Hong, et al., 2011). Similarly, in HNSCC, low doses of 5-fluorouracil and cisplatin increased tumor cell release of IL-6 and G-CSF, as well as reduced IL-1 β levels. In this study, primary tumor cells displayed chemotherapy-induced upregulation of Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Tumor necrosis factor α (TNF α), though 5-fluorouracil and cisplatin led to a decline in GM-CSF and TNF α levels in metastatic tumor cells (Reers, et al., 2013).

In PDAC, gemcitabine treatment can enhance the release of several T-cell attracting cytokines both *in vitro* and *in vivo*. These include several CCL, CXCL, and IL family members, as well as several components of the TGF β pathway (Principe, et al., 2020). In breast cancer cells, paclitaxel and docetaxel induced TNF α biosynthesis in a toll-like receptor 4 (TLR4)-dependent mechanism (Sprowl, et al., 2012). Similar results have been observed in other cell lines, and the authors concluded that taxane-induced inflammatory cytokine production is dependent on the duration of exposure and is mechanistically distinct from LPS-induced cytokine production (Edwardson, et al., 2017). A similar study explored the effects of cyclophosphamide in tumor cells and showed that cyclophosphamide treatment led to an acute secretory activating phenotype characterized by increased release of CCL4, IL8, VEGF, and TNF α . These paracrine factors enhanced macrophage infiltration and phagocytic activity, suggesting that chemotherapy can increase the tumoricidal effects of the innate immune system by altering local cytokine levels (Pallasch, et al., 2014). Cyclophosphamide has also been shown to enhance the expression of GM-CSF, IL-1 β , IL-7,

IL-15, IL-2, IL-21, and IFN γ , thereby potentiating anti-tumor immune responses (Bracci, et al., 2007). Also related to IFN signals, a recent study has demonstrated that anthracycline-based chemotherapy stimulates the rapid production of type I IFNs following activation of TLR3. This leads to enhanced levels of CXCL10 within the breast tumor microenvironment, enhancing local immune responses. The authors concluded that chemotherapy could mimic sterilizing immune responses, which may constitute a hallmark of successful chemotherapy (Sistigu, et al., 2014). Additional research suggests that this response can be potentiated through STAT3 inhibition, which may also be of clinical utility (Yang, et al., 2015).

It is important to note that ovarian tumor cell debris induced by cisplatin or paclitaxel stimulated macrophage release of pro-inflammatory cytokines and bioactive lipids, thereby enhancing tumorigenesis. This was abrogated through pharmacologic inhibition of cyclooxygenase-2 (COX-2) and soluble epoxide hydrolase (sEH) pathways, suggesting that the effect of chemotherapy on local immune cues is both complex and context-specific (Gartung, et al., 2019). Additionally, chemotherapy-induced cytokine production has been implicated in chemotherapy-associated cognitive impairment (Cheung, et al., 2015; Ren, St Clair, & Butterfield, 2017). Hence, while chemotherapy-induced alterations to the tumor secretome may offer potential avenues for combination therapy, these and other adverse effects should be considered.

6 – LYMPHOCYTE TRAFFICKING, DIFFERENTIATION, AND EFFECTOR FUNCTION

Consistent with observations that select chemotherapies can alter tumor cytokine production, several studies have also identified a relationship between chemotherapy and tumor-infiltrating immune cell populations. For example, an early report in breast cancer determined that patients receiving neoadjuvant paclitaxel had enhanced tumor-infiltrating lymphocytes, the degree of which correlated with therapeutic responses (Demaria, et al., 2001). Several studies have also suggested that chemotherapy-induced immune responses are predictive of favorable outcomes, with most focusing on breast cancer. For example, breast cancer patients with a high CD8⁺ and low FoxP3 infiltrates have markedly improved overall survival following neoadjuvant treatment (Ladoire, et al., 2011). This has been confirmed through other studies, all suggesting that local immune responses may be a cornerstone of the anti-tumor effects of chemotherapy (Asano, et al., 2017; Denkert, et al., 2010; H. Lee, Lee, Seo, Gong, & Lee, 2020; Ono, et al., 2012; Sasada, et al., 2020; K. Wang, Xu, Zhang, & Xue, 2016; N. R. West, et al., 2011). Comparable results have been observed in other disease histologies, including but not limited to colon, esophageal, ovarian, and pancreatic cancers (Cha, Park, Baik, Lee, & Kang, 2019; Fukuoka, et al., 2019; Lo, et al., 2017; Morris, Platell, & Iacopetta, 2008; Nejati, et al., 2017; Shibusaki, et al., 2018).

Consistent with these observations, beyond modulating the immunogenicity of tumor cells, several chemotherapy agents directly affect leukocytes, most notably T-cells. As discussed, much of the early rationale for chemo-immunotherapy stemmed from observations that cyclophosphamide can deplete tumor-associated Tregs and improve responses to immunotherapy by favoring effector T-cell responses. In addition to cyclophosphamide,

many other chemotherapy agents also selectively target Tregs, favoring effector CD4+ T-cell responses (Roselli, et al., 2013). For example, docetaxel treatment increased the ratio of either CD4+ or CD8+ T-cells to Tregs in patients with metastatic breast cancer, with similar results observed in NSCLC patients treated with cisplatin and vinorelbine (Roselli, et al., 2013). Accordingly, lung cancer patients who received four cycles of docetaxel-based chemotherapy showed fewer peripheral Tregs than present at baseline (J. Y. Li, et al., 2014). In metastatic colon cancer, the multidrug regimens FOLFOX (5-FU, leucovorin, and oxaliplatin) and FOLFIRI (5-FU, leucovorin, and irinotecan) also significantly reduced peripheral blood Tregs (Maeda, et al., 2011). Gemcitabine has also been shown to deplete T-cells in both humans and mice, as well as enhance the effector function of vaccine-specific CD8+ T-cells (Rettig, et al., 2011), with similar results observed in lung cancer patients (C. Chen, et al., 2015).

In addition to shifting the balance between Tregs and effector T-cells, several chemotherapy agents appear to directly alter T-cell function. For example, oxaliplatin has been shown to reduce spleen size and cellularity in BALB/c mice yet increased the relative frequency of pan-CD4+ and CD8+ T-cells, Tregs, and increased levels of TNF α . The authors presumed this was due to selective depletion of B-cells, thereby allowing for T-cell dominance (Stojanovska, et al., 2019). Further, the FOLFOX regimen (5-FU, leucovorin, and oxaliplatin) has been shown to depend on CD8+ T-cell responses to control tumor growth *in vivo*. The authors identified that FOLFOX-enabled tumor-infiltrating lymphocytes have a functional differentiation state characterized by lower levels of immune checkpoints PD-1 and TIM-3, and that T-cells from FOLFOX-treated tumors have improved effector function. They concluded that FOLFOX promotes a functional shift from an exhausted to functional T-cell phenotype (Guan, et al., 2020).

Similar results have been observed with cisplatin, as tumor-bearing mice treated with cisplatin demonstrated increased tumor CD8+ T-cell infiltration (Wakita, et al., 2019). Accordingly, cisplatin cooperated with immune checkpoint inhibition (Wakita, et al., 2019) and has similarly been shown to enhance CD8+ T-cell responses induced by DNA vaccination (Tseng, et al., 2008). These and other studies have suggested that the therapeutic efficacy of cisplatin is dependent on CD8+ T-cell activation and sustained by CD80/86-mediated co-stimulation (Beyranvand Nejad, et al., 2016; Wakita, et al., 2019).

Several other medications also alter T-cell responses. Though paclitaxel is known to increase the T-cell-activating ability of ovarian cancer cells (Tsuda, et al., 2007), additional evidence supports more direct mechanisms through which paclitaxel can enhance T-cell function, particularly in combination platinum-based agents. In NSCLC, paclitaxel, carboplatin, and bevacizumab directly enhanced CD8+ T-cell proliferation, notably for effector and memory subsets (de Goeje, et al., 2019). In cervical cancer, neoadjuvant paclitaxel and cisplatin reduced the tumor infiltration of Tregs and increased the accumulation of active CD8+ cells, though no change was observed with cisplatin alone (Heeren, et al., 2019). In metastatic melanoma patients, paclitaxel and carboplatin were able to overcome clinical resistance to anti-PD-1 therapy, associated with an increase in a subset of tumor-reactive CD8+ effector T-cells. Subsequent *in vitro* experiments determined that incubation with chemotherapy potentiated the cytotoxic function of these T-cells, supporting a direct stimulatory role for

these agents in isolated T-cells (Yan, Dronca, Liu, Markovic, & Dong, 2017). Accordingly, low dose paclitaxel has been shown to support therapeutic vaccination with melanoma antigens in mice (Sevko, et al., 2012).

Gemcitabine also appears to have direct effects on T-cell biology, though our understanding of these actions is still emerging. Following a transient reduction in absolute lymphocytes, gemcitabine may decrease the presence of memory T-cells while also promoting naive T-cell activation in PDAC (Plate, Plate, Shott, Bograd, & Harris, 2005). However, subsequent studies suggest that gemcitabine may also impede T-cell activation, suppressing proliferation and inducing apoptosis in a T-cell subtype and dose-dependent manner (Glenn, Xue, & Whartenby, 2018; Smith, Yogaratnam, Samad, Kasow, & Dalglish, 2021). While these and other chemotherapy agents have been shown to contextually promote T-cell function, it is important to note that chemotherapy has long been known to cause lymphopenia over time (Aldarouish, et al., 2019; Grossman, et al., 2015; Lissoni, Fumagalli, Paolorossi, & Mandala, 1999; Menetrier-Caux, Ray-Coquard, Blay, & Caux, 2019; Verma, et al., 2016). Hence, the proper dose and duration of these and other immune-stimulating chemotherapies warrants continued investigation.

7 – CHEMOTHERAPY AND OTHER IMMUNE CELL POPULATIONS

While T-cells have become the primary focus in cancer immunotherapy due to their capacity to kill tumor cells (Coulie, Van den Eynde, van der Bruggen, & Boon, 2014; Galon, et al., 2006), several additional leukocyte subtypes are critical for therapeutic responses. Though the effects of chemotherapy on these immune cell subsets are less studied than the more classic mediators of sterilizing immunity, emerging data suggests that several chemotherapy agents modulate the effects of several additional leukocytes. Much of this data pertains to macrophages and natural killer (NK) cells, both of which are briefly discussed below.

7.1 – Macrophage Recruitment and Polarization

Macrophages are central to therapeutic responses to immune checkpoint inhibition (DeNardo & Ruffell, 2019), and several recent studies now suggest that several aspects of macrophage biology are impacted by cytotoxic chemotherapy. Several studies have explored the effects of docetaxel on macrophages and myeloid-derived suppressor cells (MDSCs). Very early reports demonstrated that cyclophosphamide, doxorubicin, and paclitaxel enhance the anti-tumor immune response of GM-CSF-secreting whole-cell vaccines in murine models of breast cancer, in part through potentiating Th1 responses (Machiels, et al., 2001) that can enhance the tumoricidal effects of macrophages (T. Li, Wu, Yang, Zhang, & Jin, 2020). More recently, vincristine, cyclophosphamide, and doxorubicin have been shown to cooperate with a CD40-agonist and cytosine-phosphate-guanosine-containing oligodeoxynucleotide 1826 (CpG-ODN) immunotherapy regimen through the repolarization of tumor-associated macrophages (Buhtoiarov, et al., 2011). Similarly, incubation with cyclophosphamide metabolites enhanced the production of pro-inflammatory cytokines IL-6 and IL-12 and down-regulated the suppressive cytokines IL-10 and TGF β in mouse peritoneal macrophages (Bryniarski, Szczepanik, Ptak, Zemelka, & Ptak, 2009), and

cyclophosphamide-educated peritoneal macrophages have been shown to protect effector T-cells from suppression (Majewska-Szczepanik, et al., 2018).

The effects of other chemotherapy agents on macrophage biology are highly varied and context-dependent. Docetaxel has several effects on monocyte-derived cell populations. Incubation with docetaxel re-polarized MDSCs toward an M1-like phenotype (Kodumudi, et al., 2010). This is consistent with other observations suggesting that docetaxel promotes the generation of anti-tumorigenic human macrophages, promotes the differentiation of immature monocytes into M1 macrophages, and increases the antigen presentation capacity of myeloid cells. (Millrud, Mehmeti, & Leandersson, 2018). Cisplatin also appears to prime peritoneal macrophages for enhanced expression of several inflammatory cytokines and transcription factors upon co-culture with murine fibroblasts (Chauhan, Sodhi, & Shrivastava, 2009).

However, taxane and non-taxane neoadjuvant chemotherapy have been shown to enhance the recruitment of Tie2+ macrophages in breast cancer, facilitating the entry of tumor cells into circulation and promoting metastasis (Karagiannis, et al., 2017). Human peripheral blood monocytes co-cultured with esophageal SCC cells treated with 5-FU and cisplatin shifted macrophages toward a more immune suppressive, CD163+ phenotype in an IL-34-dependent mechanism (Nakajima, et al., 2021). Similarly, ovarian tumor cells treated with platinum-based agents also induced an immune-suppressive M2 phenotype in adjacent macrophages, which was reversed by either COX or IL-6 inhibition (Dijkgraaf, et al., 2013). Though gemcitabine can deplete MDSCs (Eriksson, Wenthe, Irenaeus, Loskog, & Ullenhag, 2016), conditioned media from PDAC cells treated with gemcitabine shifts macrophages toward an M2 phenotype, characterized by increased expression of arginase-1 and TGF β 1 (Deshmukh, et al., 2018). Thus, the effects of chemotherapy on macrophage function are varied, with these and other studies suggesting both immune-stimulating and immune-suppressive effects. Given the roles of macrophages and MDSCs in cancer immunotherapy, this is an important area that warrants further study.

7.2 – Natural Killer Cells

Though cytotoxic T-cells are considered the main effector cells in most cancer immunotherapies, the importance of NK cells is now recognized (Shimasaki, Jain, & Campana, 2020). Several chemotherapy agents have been shown to modulate NK cell function, and like macrophages, the results are often contradictory and context-dependent. For example, gemcitabine enhances NK cell-mediated cytotoxicity (Okita, et al., 2015), and increases NK cell proliferation (Dammeijer, et al., 2021). Accordingly, low-dose gemcitabine treatment enhances NK cell-mediated anti-tumor immunity in lung cancer (Zhang, et al., 2020), and the combination of gemcitabine and cytokine-activated NK cells has shown preclinical promise in HCC (Morisaki, et al., 2011). Also supporting an activating role for chemotherapy, metronomic dosing with cyclophosphamide enhances NK cell effector function in end-stage cancer patients (Ghiringhelli, et al., 2007), and cisplatin appears to enhance NK cell function by enhancing tumor cell expression of MHC class I chain-related molecule A and B (Okita, et al., 2016).

However, several studies have reported that chemotherapy can suppress NK cell function. Notable examples include the observation that paclitaxel inhibits the binding of NK cells to their targets through the down-regulation of adhesion molecules (Loubani & Hoskin, 2005). Similarly, paclitaxel and vinblastine downregulate CD11a and CD54 expression in P815 mastocytoma cells, conferring resistance to killing by non-specific killer lymphocytes (Zhao, Morgan, Haeryfar, Blay, & Hoskin, 2003). Hence, this area also warrants additional exploration, particularly as NK cell-centric therapies advance in the clinic.

8 – CLINICAL ADVANCES IN CHEMO-IMMUNOTHERAPY

In light of the mounting preclinical evidence described above, several recent clinical trials have explored novel combinations of chemotherapy and ICI-based immunotherapy. Although a comprehensive list of these trials is beyond the scope of this review, several are showing considerable promise. Here we discuss select major trials in this rapidly evolving field, with a particular emphasis on those that have been evaluated in phase 3 trials and/or approved by the FDA.

8.1 – Lung Cancer

The anti-PD-1 antibody pembrolizumab has revolutionized the treatment landscape for NSCLC, both as a single agent for patients with high PD-L1 expression and in combination with chemotherapy (Reck, et al., 2016). Recent evidence has solidified the concept that pembrolizumab may synergize with chemotherapy in NSCLC. Based on encouraging phase 2 data (Langer, et al., 2016), a large phase 3 trial has recently evaluated the anti-PD-1 antibody pembrolizumab as a monotherapy or in combination with pemetrexed and platinum-based chemotherapy in untreated patients with metastatic, non-squamous NSCLC without sensitizing EGFR or ALK mutations. After one year, the median overall survival for the combination group was 69.2% compared to 49.4% for the monotherapy group. The survival benefit of the combination treatment was observed across all patients independent of PD-L1 status, with clinically meaningful improvements in median overall survival for patients in the combination arm (Gandhi, et al., 2018). In squamous NSCLC, the combination of pembrolizumab, carboplatin, and paclitaxel or nab-paclitaxel was also effective, independent of PD-L1 status. Combination immunotherapy led to a median overall survival of 15.9 months compared to 11.3 months for chemotherapy alone, extending median progression-free survival to 6.4 months compared to 4.8 months for the chemotherapy group (Paz-Ares, et al., 2018). Based on these and related studies, pembrolizumab, in combination with pemetrexed and platinum-based chemotherapy, was approved in 2018 as a first-line treatment for metastatic, non-squamous NSCLC lacking EGFR or ALK mutations.

Similar regimens are also under evaluation, notably the combination of carboplatin, pemetrexed, and the anti-PD-1 antibody camrelizumab, show promising results based on interim analysis in a phase 3 trial (C. Zhou, et al., 2021). Similar results have been observed in extensive-stage small-cell lung cancer (SCLC), where the addition of atezolizumab to carboplatin and etoposide resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (Horn, et al., 2018). The combination

of the anti-PD-1 antibody durvalumab and platinum and etoposide chemotherapy has also been evaluated as a first-line treatment for extensive-stage SCLC. This approach showed improved overall survival compared to chemotherapy alone, extending median overall survival from 10.3 to 13 months (Paz-Ares, et al., 2019).

In addition to showing efficacy as a first-line therapy (Table 3), ICI-based immunotherapy is showing promise as a second-line treatment in NSCLC. For example, the anti-PD-1 antibody nivolumab has been combined with platinum-based doublet chemotherapy (cisplatin or carboplatin plus either gemcitabine, pemetrexed, or paclitaxel) with encouraging results (Rizvi, et al., 2016). The anti-PD-L1 antibody avelumab showed substantial activity in patients with progressive or platinum-resistant metastatic or recurrent disease. Of the 184 patients enrolled, 22 demonstrated objective clinical responses and 70 had stable disease, for an overall disease control rate of 50% (Gulley, et al., 2017). Though early phase 2 data suggested that subsequent-line avelumab may be more efficacious than docetaxel (Fehrenbacher, et al., 2016), more recent phase 3 data suggest that avelumab does not improve survival beyond docetaxel but has a favorable toxicity profile (Barlesi, et al., 2018). After two years of follow-up, the authors concluded that avelumab did not significantly prolong overall survival compared to docetaxel in patients with platinum-treated, PD-L1-expressing NSCLC (K. Park, et al., 2021).

The anti-PD-L1 antibody atezolizumab has also been explored in previously treated NSCLC, extending survival beyond that observed with second-line docetaxel (Rittmeyer, et al., 2017). The combination of atezolizumab, carboplatin, and nab-paclitaxel has since been evaluated in NSCLC as a first-line treatment, particularly for those with stage IV disease and no ALK or EGFR mutations. This combination showed substantial therapeutic efficacy, extending median overall survival to 18.6 months compared to 13.9 months with chemotherapy alone (H. West, et al., 2019). The combination of atezolizumab, carboplatin, and nab-paclitaxel has also been combined with the VEGF-inhibiting antibody bevacizumab. As a first-line treatment, this combination regimen led to a median overall survival of 19.2 months, compared to 14.7 months for bevacizumab and chemotherapy only (Socinski, et al., 2018). In patients with baseline liver metastases, this combined regimen was similarly effective, extending median overall survival to 13.3 months compared to 9.4 months for patients receiving bevacizumab and chemotherapy only (Reck, et al., 2019). Several other combination strategies are also being evaluated in clinical trials for NSCLC, as well as for other forms of lung cancer.

8.2 – Head & Neck Cancer

Chemo-immunotherapy has been evaluated extensively in HNSCC. For example, pembrolizumab plus platinum-based chemotherapy and 5-FU has been highly effective in patients with untreated locally incurable recurrent or metastatic HNSCC. A recent phase 3 study demonstrated that pembrolizumab and platinum plus 5-FU chemotherapy is superior to either single-agent pembrolizumab or cetuximab and chemotherapy. Importantly, this approach was non-inferior for all patients regardless of PD-L1 expression. Based on these data, this approach is now FDA approved and is recommended as an appropriate first-line treatment for PD-L1+ recurrent or metastatic HNSCC (Burtneess, et al., 2019).

Both pembrolizumab and nivolumab have also been evaluated as a second-line treatment option for platinum-refractory HNSCC. Pembrolizumab was explored in a single-arm phase 2 study for patients with platinum- and cetuximab-refractory HNSCC, showing clinically meaningful anti-tumor activity and an acceptable safety profile (Bauml, et al., 2017). In a larger phase 3 study, pembrolizumab was also evaluated for HNSCC patients who progressed during or after treatment with platinum chemotherapy for recurrent or metastatic disease, demonstrating significant anti-tumor activity reflected by meaningful improvements in overall survival (Cohen, et al., 2019). Consequently, the FDA has approved pembrolizumab for use in this indication for all patients.

Similar results have been observed using nivolumab, which has also been evaluated in patients with recurrent or metastatic HNSCC who had experienced disease progression within 6 months of receiving platinum-based chemotherapy. This approach has now been evaluated in a phase 3 trial, where nivolumab extended median overall survival to 7.5 months compared to 5.1 months with chemotherapy alone (Ferris, et al., 2016). Subsequent evaluation has confirmed that nivolumab has superior therapeutic efficacy than the previous standard of care chemotherapy, which was unrelated to prior cetuximab exposure (Ferris, et al., 2019). Based on these data, nivolumab has also been approved by the FDA for this indication.

Though these and other studies have shown considerable promise, others have posted negative results. For example, in locally advanced HNSCC, the combination of avelumab, cisplatin, and radiation therapy did not meet the primary objective of prolonging progression-free survival (N. Y. Lee, et al., 2021). Similarly, durvalumab with or without tremelimumab failed to improve clinical outcomes beyond cetuximab and chemotherapy (Ferris, et al., 2020).

8.3 – Gastro-Esophageal Cancer

Combined chemo-immunotherapy has shown rapid progress for gastro-esophageal cancers in recent years, with several approaches earning FDA approval. In advanced, HER2 negative gastric, gastro-esophageal junction (GEJ), or esophageal adenocarcinoma, nivolumab and FOLFOX showed superior overall survival compared to FOLFOX alone. The combination arm demonstrated a median overall survival of 13.1 months compared to 11.1 months for chemotherapy alone. As nivolumab and chemotherapy showed superior overall and disease-specific survival (Y. Y. Janjigian, et al., 2021), this combined regimen has now been FDA approved for initial treatment of advanced/metastatic gastric, GEJ, and esophageal adenocarcinomas, irrespective of PD-L1 expression.

Pembrolizumab has also been evaluated extensively in gastro-esophageal cancers, including in combination with chemotherapy. A recent phase 3 trial compared single-agent pembrolizumab with pembrolizumab and cisplatin plus 5-FU or capecitabine for patients with untreated, advanced gastric/GEJ cancers and found that pembrolizumab was non-inferior to chemotherapy. This study determined that the combination of pembrolizumab and chemotherapy is not superior to pembrolizumab alone (Shitara, et al., 2020). However, a more recent phase 3 study determined that the combination of pembrolizumab, cisplatin, and 5-fluorouracil was highly effective as a first-line treatment. This approach was superior

to chemotherapy alone, extending median overall survival from 8.8 months to 13.9 months for PD-L1+ patients and from 9.8 months to 12.4 months for all randomized patients (Sun, et al., 2021). Based on these data, this approach has also been approved by the FDA.

Additional trials have explored similar combinations for HER2+ gastro-esophageal cancer. Importantly pembrolizumab is under investigation in combination with trastuzumab and platinum and fluoropyrimidine chemotherapy for patients with locally advanced or metastatic gastric or gastro-esophageal junction cancer that is not amenable to surgical resection or definitive chemo-radiation. Though only interim results for the first 264 patients have been presented, the addition of pembrolizumab improved the response rate from 52 to 74%, with evidence of durable anti-tumor efficacy (Yelena Y. Janjigian, et al., 2021). This led to the accelerated FDA approval of this regimen in 2021.

Several immunotherapy approaches have been evaluated following progression on chemotherapy. Early data suggested that pembrolizumab has significant anti-tumor activity in metastatic esophageal cancer patients who have progressed on at least two prior lines of therapy (Doi, et al., 2018). Similar results were observed in a phase 2 trial (Shah, et al., 2019), as well as in a subsequent study for previously treated advanced gastric or GEJ cancers (Fuchs, et al., 2018). This was confirmed in a larger phase 3 study, where pembrolizumab was superior to paclitaxel, docetaxel, or irinotecan as a second-line treatment for patients with advanced/metastatic esophageal cancer (Kojima, et al., 2020).

Nivolumab has shown similar efficacy in treatment-refractory esophageal cancer (Kudo, et al., 2017), as well as for advanced, treatment-refractory gastric or gastro-esophageal cancer (Y.-K. Kang, et al., 2017). In a phase 3 trial, nivolumab was again highly effective in advanced gastric or GEJ cancers refractory to at least two previous chemotherapy regimens, increasing 12-month overall survival from 10.9% with placebo to 26.2% (Y. K. Kang, et al., 2017). The combination of nivolumab and ipilimumab has also been evaluated as a second-line treatment in advanced gastric or GEJ cancers. This approach led to improved responses compared to nivolumab monotherapy, though phase 3 studies have yet to share results (Janjigian, et al., 2018). The anti-PD-1 antibody camrelizumab has also shown promise as second-line therapy for Chinese patients with metastatic esophageal cancer. This phase 3 trial only included patients with squamous histology, and camrelizumab led to significant improvements in overall survival compared to second-line chemotherapy (Huang, et al., 2020). Avelumab has been explored in chemotherapy-treated advanced gastric or GEJ cancers, particularly as first-line switch-maintenance therapy or second-line treatment. However, the clinical benefit achieved with avelumab has been marginal, and the approved treatment options are preferred (Chung, et al., 2019).

8.4 – Urothelial Cancer

In urothelial cancer, pembrolizumab is now FDA approved as a first-line treatment for PD-L1+ patients not eligible for platinum-based chemotherapy (Balar, Castellano, et al., 2017). Similarly, pembrolizumab has shown promise for platinum-refractory advanced urothelial carcinoma, with improved survival and fewer treatment-related adverse events than chemotherapy with paclitaxel, docetaxel, or vinflunine (Bellmunt, et al., 2017). Nivolumab has shown similar efficacy as a second-line treatment irrespective of PD-L1

status (Sharma, et al., 2017). Atezolizumab was granted accelerated approval by the FDA for platinum-refractory urothelial carcinoma based on single-arm phase 2 data (Balar, Galsky, et al., 2017). However, subsequent phase 3 data has since demonstrated that atezolizumab was not associated with significantly longer overall survival than chemotherapy in this indication (Powles, et al., 2018). Based on these observations, the FDA has withdrawn approval for atezolizumab in patients with advanced, platinum-refractory urothelial carcinoma. Other approaches have also been explored in clinical trials, including avelumab for metastatic, platinum-refractory urothelial carcinoma. In this study, avelumab showed superior progression-free survival compared to chemotherapy alone (Patel, et al., 2018). This led to the FDA approval for avelumab, though it is important to note that these conclusions were drawn from expansion cohorts of phase 1 trials and that phase 3 studies are still pending.

Despite these observations, progress has been difficult for chemo-immunotherapy in urothelial cancer. The combination of atezolizumab and platinum-based chemotherapy is under investigation and has shown superior progression-free survival compared to chemotherapy alone (Galsky, et al., 2020). However, the addition of the anti-PD-1 antibody pembrolizumab to first-line platinum-based chemotherapy (gemcitabine and either cisplatin or carboplatin) did not significantly improve clinical outcomes, and the authors suggested that this approach should not be adopted for the treatment of advanced urothelial carcinoma (Powles, et al., 2021). Hence, this area warrants continued exploration in urothelial carcinoma.

8.5 – Breast and Ovarian Cancers

Several trials are also evaluating chemo-immunotherapy in breast and ovarian cancers. A recent multicenter trial has explored the efficacy of atezolizumab and nab-paclitaxel in patients with unresectable, locally advanced, or metastatic triple-negative breast cancer (TNBC). In patients with advanced disease, this combination extended median progression-free survival to 7.2 months compared to 5.5 months in the nab-paclitaxel group (Schmid, et al., 2018). In the second analysis, the addition of atezolizumab to nab-paclitaxel marginally improved median overall survival from 18.7 to 21 months, though for PD-L1+ tumors, median overall survival was 25 months compared to 18 months with placebo (Schmid, Rugo, et al., 2020). Patient-reported outcomes suggest that this approach was reasonably well tolerated, without compromising the patients' health-related quality of life (Adams, et al., 2020). However, a similar trial explored the combination of neoadjuvant atezolizumab with anthracycline, cyclophosphamide, and taxane-based chemotherapy in early-stage TNBC. In this group, 58% of patients in the combination arm had pathologic complete responses to treatment compared to 41% for patients with chemotherapy alone. For PD-L1+ tumors, 69% of patients in the combination arm had pathologic complete responses, as did 49% for patients receiving chemotherapy alone (Mittendorf, et al., 2020).

Importantly, pembrolizumab has been evaluated in combination with neoadjuvant paclitaxel and carboplatin for early-stage TNBC. At the first interim analysis, 64.8% of patients in the combination arm demonstrated pathologic complete responses compared to 51.2% with chemotherapy and placebo. After 15.5 months, 7.4% of patients in the pembrolizumab,

paclitaxel, and carboplatin group and 11.8% in the control group experienced disease progression precluding definitive surgery, demonstrated clinical recurrence, or died from any cause (Schmid, Cortes, et al., 2020). This led to the FDA approval of pembrolizumab in combination with neoadjuvant chemotherapy for early-stage TNBC in 2021. In a related study, pembrolizumab was administered to patients with metastatic TNBC in combination with nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin. This study also considered PD-L1 expression, and the combination of pembrolizumab and chemotherapy showed a significant improvement in progression-free survival compared to the control group, particularly for PD-L1 expressing tumors (Cortes, et al., 2020). This approach was initially given accelerated approval by the FDA in 2020, but converted to full approval in 2021.

Though these and other important trials are encouraging, progress for immunotherapy in ovarian cancer has been difficult. For instance, avelumab failed to improve either progression-free or overall survival in platinum-resistant or platinum-refractory ovarian cancer, either as a monotherapy or combined with pegylated liposomal doxorubicin (Pujade-Lauraine, et al., 2021). Additionally, avelumab failed to show significant efficacy as front-line therapy in ovarian cancer, even when combined with carboplatin and paclitaxel (Monk, et al., 2021). Pembrolizumab has shown only modest activity in monotherapy for patients with advanced, recurrent ovarian cancer, with higher response rates in patients with PD-L1+ disease (Matulonis, et al., 2019). Pembrolizumab has also been studied in combination with bevacizumab and oral metronomic cyclophosphamide, also in recurrent ovarian cancer, though early data suggests an objective response rate of 47.5% with a median progression-free survival of 10.0 months (Zsiros, et al., 2021).

8.6 – Pancreatic Cancer

Several combinations of chemo- and immunotherapy have been explored in PDAC, in large part attributed to poor disease control rates using either approach alone (Principe, et al., 2021). For example, the combination of gemcitabine and the anti-CTLA-4 antibody tremelimumab showed an overall response rate of 10.5%, with 2/19 patients achieving a partial response and a median overall survival of 7.4 months (Aglietta, et al., 2014). Similarly, gemcitabine and the anti-CTLA-4 antibody ipilimumab led to a disease control rate was 43%, though median progression-free survival was 2.5 months, and median overall survival 8.5 months (Kalyan, et al., 2016). This approach has been explored in a different patient cohort, with similar results of a median overall survival of 6.9 months, progression-free survival of 2.8 months, and an overall response rate was 14%. Of the three responding patients, one showed a complete response, with a median response duration of 11 months (Kamath, et al., 2019).

Similarly, a phase 1 trial explored the combination of the anti-PD-1 antibody nivolumab with chemotherapy. This study consisted of two arms: patients who had received one prior chemotherapy regimen and treatment-naïve patients. Previously treated patients were administered nivolumab and nab-paclitaxel, and treatment-naïve patients nivolumab, nab-paclitaxel, and gemcitabine. In previously treated patients, 2/9 had a partial response and 4/9 had stable disease, for a disease control rate of 66.6%. For the treatment-naïve patients, 3/6 had a partial response and 3/6 had stable disease (Wainberg, et al., 2017). In an extended

Phase 1 study of a larger cohort of treatment-naïve patients, the combination of nivolumab, nab-paclitaxel, and gemcitabine led to 1/50 complete response, 8/50 partial responses, and 23/50 patients with stable disease. Median progression-free survival in this group was 5.5 months, with a median overall survival of 9.9 months. However, this combination was poorly tolerated, with 48/50 patients had at least 1 grade 3/4 treatment-related adverse event (Wainberg, et al., 2019).

Pembrolizumab has also been explored in combination with chemotherapy in PDAC. In a seminal study, 2/11 PDAC patients showed a partial response, with a median overall survival of 8.0 months (Weiss, et al., 2017). A phase 2 study from the same group evaluated the combination of pembrolizumab, gemcitabine, and nab-paclitaxel in patients with metastatic PDAC as a first-line treatment. The authors observed a disease control rate of 100%, with 3/11 patients showing a partial response and the remaining 8/11 showing stable disease. Overall survival was 15.0 months and progression-free survival 9.1 months, though the primary endpoint of a 15% complete response rate was not met. (Weiss, et al., 2018).

Other combinations have also been evaluated, including cisplatin, gemcitabine, nab-paclitaxel, and pembrolizumab. Of the 25 metastatic PDAC patients in this study, 15/24 patients had a partial response and 4/24 had stable disease, with a median overall survival of 16.5 months. (Jameson, et al., 2017). The combination of gemcitabine, nab-paclitaxel, durvalumab, and tremelimumab is also showing promise, with preliminary findings from 11 patients reporting a disease control rate of 100%, with 8/11 patients demonstrating a partial response. (Renouf, et al., 2018). The combination of durvalumab and the TGF β receptor inhibitor galunisertib has also been evaluated in a phase 1b trial, specifically for patients with metastatic PDAC that have progressed on two prior lines of chemotherapy. This led to an overall disease control rate of 25%, and the authors suggested that this approach may have improved efficacy either as an earlier line of therapy or for patients with predictive biomarkers associated with TGF β signaling (Melisi, et al., 2021). These and similar combinations continue to show promise for PDAC and other difficult to treat cancer types, and pending additional study, may either improve outcomes beyond the current standard-of-care or offer an effective treatment strategy in the second or third-line setting.

9 – SUMMARY AND FUTURE DIRECTION

Though long considered immunosuppressive, there is mounting evidence to support select immune-stimulating properties of cytotoxic chemotherapy. Accordingly, several chemo-immunotherapy regimens are now regularly used in cancer therapy, with many others showing promise in clinical trials. Though these approaches have shown rapid progress for select cancers, for others, progress has been difficult. As the field has reached consensus regarding the promise of cancer immunotherapy for difficult-to-treat cancer histologies, the immunomodulatory effects of chemotherapy warrant continued investigation to design the most effective combination strategies.

Based on studies described in this review, it appears as though the immune-stimulating effects of several chemotherapy agents are often predictable, consistently directing many of the same immune cell processes across a wide range of tumor types. Should certain

chemotherapy medications indeed have predictable patterns of immune remodeling, this opens the possibility that these can be exploited for therapy through tailored combination strategies. Such approaches have already shown early promise in preclinical experiments, taking advantage of chemotherapy-enhanced antigen presentation and incorporating selective inhibition of local chemotherapy-induced immune suppression within the tumor microenvironment (Principe, et al., 2020). Recent evidence also supports that such combinations of chemo- and immunotherapy may further benefit from refinement of drug delivery and timing, including sequential administration with different waves, spatial delivery, or co-delivery strategies (Luo, Zhang, Luo, & Jiang, 2019). Hence, this area warrants continued investigation.

However, it important to note that select chemo-immunotherapy approaches will require caution when translated to patient care. Bone marrow suppression is one of the most important dose-limiting toxicities associated with chemotherapy (Y. Wang, Probin, & Zhou, 2006), and the primary reason chemotherapy had previously been considered universally immune suppressive. Hence, as combination chemo-immunotherapy regimens advance in the clinic, it will be important to carefully balance the immune-stimulating effects of chemotherapy with the long-term negative effects on hematopoiesis, and alterations to dose and schedule may be indicated. Additionally, the adverse effects of immune checkpoint inhibitors can be severe, and in some cases, life-threatening (F. Martins, et al., 2019). As immune-mediated adverse events are often predictive of anti-tumor immune responses (Das & Johnson, 2019), the improved efficacy of combined chemo-immunotherapy may increase the risk of autoimmune toxicity. However, given the promise for these combination strategies, mechanisms of chemotherapy-induced immune remodeling warrant continued exploration in hopes of maximizing efficacy and improving therapeutic response rates, particularly in cancers for which there is currently no effective treatment.

ACKNOWLEDGEMENTS

This article is dedicated to the memory of our good friend Daniel J. Takala who recently passed away after a courageous battle with glioblastoma. This work was supported by NIH R01CA07059 to M. Korc, by NIH F30CA236031 and UIC Award for Graduate Research to D. R. Principe, and by NIH R01CA217907 and R21CA255291 and the Veterans Affairs Merit Award I01BX002922 to H.G. Munshi.

ABBREVIATIONS

ALK	Anaplastic Lymphoma Kinase
APCs	Antigen-presenting cells
BCG	Bacille Calmette-Guérin
CBP	CREB-binding protein
cGAS	Cyclic GMP-AMP Synthase
COX	Cyclooxygenase
COA-1	Cytochrome C oxidase assembly factor 1

CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTLs	Cytotoxic T lymphocytes
CpG-ODN	Cytosine-phosphate-guanosine-containing oligodeoxynucleotide 1826
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
dFdC	2', 2'-difluoro 2'-deoxycytidine
dMMR	DNA mismatch repair
eIF2α	Eukaryotic translation initiation factor 2 α
EGFR	Epidermal Growth Factor Receptor
ER	Endoplasmic reticulum
ERAP	ER Aminopeptidase
ERK	Extracellular signal-regulated kinase
ESCC	Esophageal squamous cell carcinoma
FOLFOX	5-FU, leucovorin, and oxaliplatin
FOLFIRI	5-FU, leucovorin, and irinotecan
GEJ	Gastro-esophageal junction
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GZMB	Granzyme B
HCC	Hepatocellular carcinoma
HLA-I	Class I Human Leukocyte Antigen
HNSCC	Head and neck squamous cell carcinoma
HMGB1	High-mobility group box 1 protein
ICIs	Immune checkpoint inhibitors
IFN	Interferon
IL	Interleukin
MHC	Major Histocompatibility Complex
MDSCs	Myeloid-derived suppressor cells

NK	Natural killer
NSCLC	Non small-cell lung cancer
MSI-H	High microsatellite instability
PDAC	Pancreatic ductal adenocarcinoma
PRF1	Perforin 1
PD-1	Programmed cell death protein 1
PD-L1	PD-1 ligand 1
PERK	Protein kinase-like ER kinase
SCLC	Small-cell lung cancer
sEH	Soluble epoxide hydrolase
STING	Stimulator of Interferon Genes
TAP	Transporters associated with Antigen Processing
TCR	T-cell receptor
TERT	Telomerase reverse transcriptase
TGFβ	Transforming Growth Factor β
TMB-H	Tumor mutational burden
TME	Tumor microenvironment
TLR	Toll-like receptor
TNBC	Triple-negative breast cancer
Tregs	Regulatory T-lymphocytes
TNFα	Tumor necrosis factor α
VEGF	Vascular Endothelial Growth Factor
5-FU	5-fluorouracil
β2m	β 2-microglobulin

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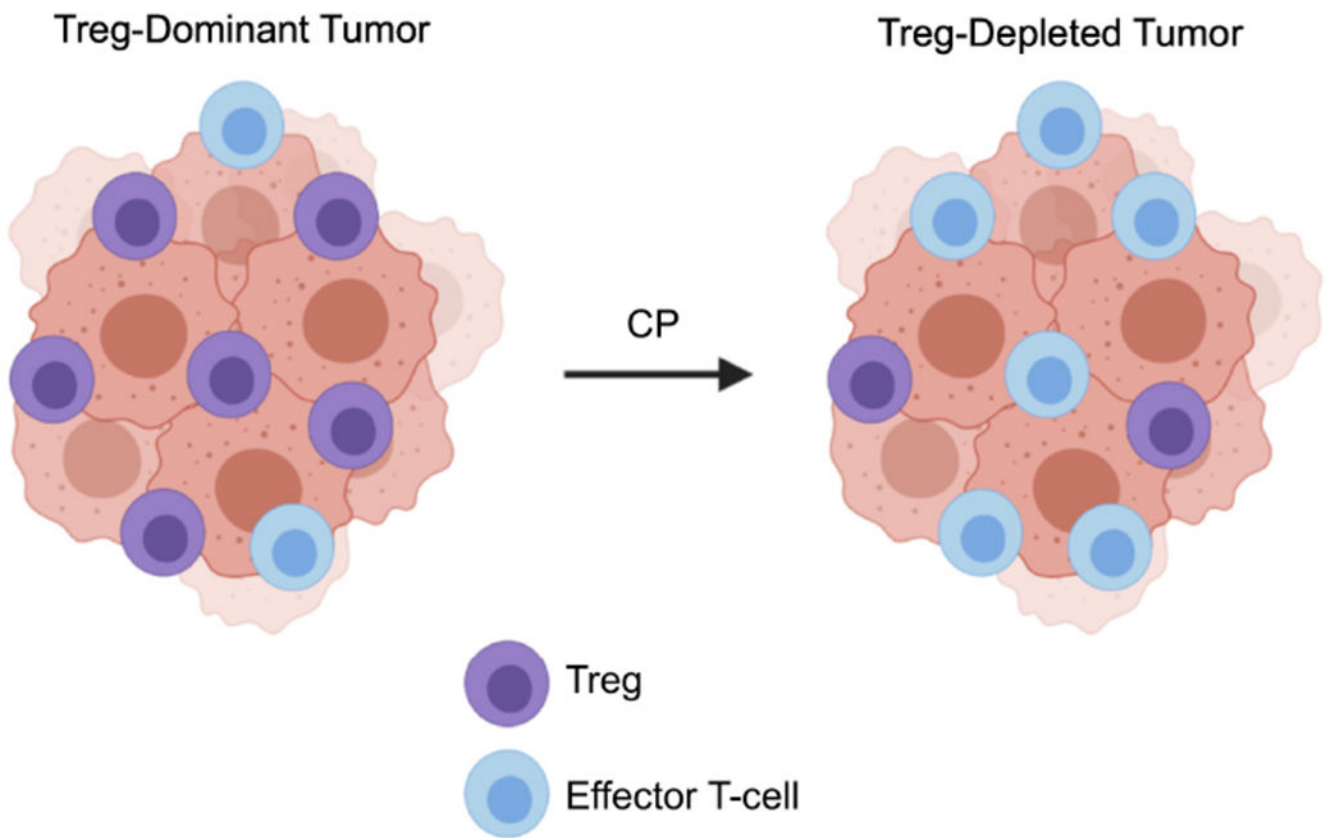


Figure 1. Cyclophosphamide-mediated depletion of regulatory T-lymphocytes.

The immunogenic effects of cyclophosphamide (CP) are well documented, and much of the early rationale for combining chemotherapy and immunotherapy stemmed from observations that cyclophosphamide chemotherapy can deplete tumor-associated regulatory T-lymphocytes (Tregs). This specialized T-cell subpopulation acts to inhibit sterilizing immune responses and maintain peripheral tolerance. Tregs are highly sensitive to cyclophosphamide compared to effector T-cells, and cyclophosphamide has long been suggested as a potential means of targeting Tregs to potentiate cancer immunotherapy.

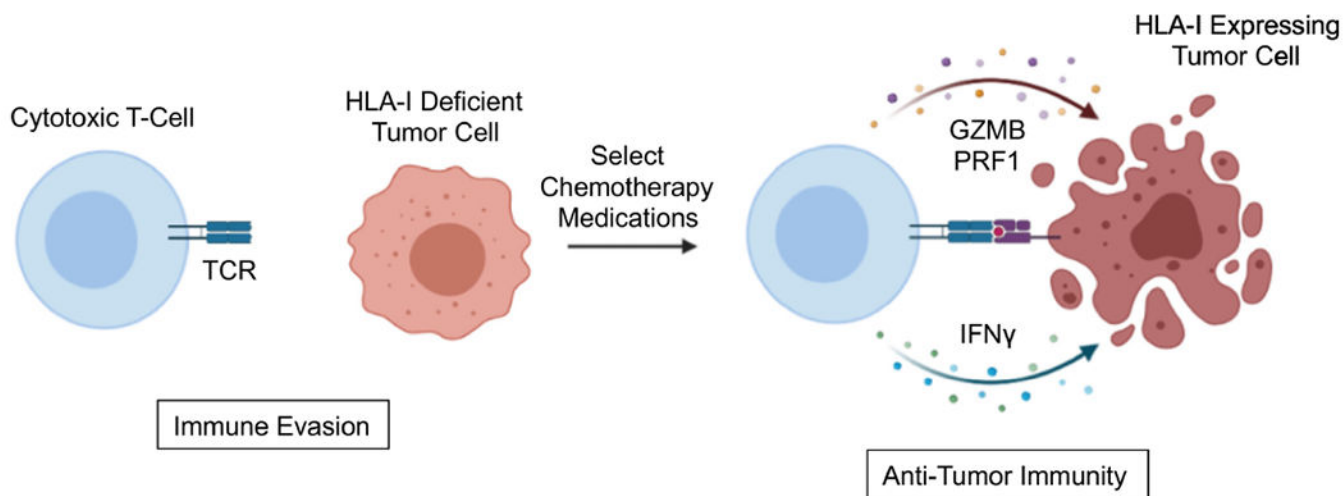


Figure 2. Chemotherapy-induced HLA Class I expression enhances anti-tumor immune responses.

The loss of HLA Class I (HLA-I) is a widely utilized mechanism for immune evasion in cancer, impeding the ability of cytotoxic T-lymphocytes to recognize and destroy tumor cells. Several chemotherapy agents have been shown to augment tumor cell expression of HLA-I. While most studies to date have focused on platinum-based medications such as cisplatin and oxaliplatin, emerging data also supports a pro-antigen presentation role for non-platinum-based chemotherapy. Thus, by increasing the expression of HLA-I on the tumor cell surface, chemotherapy can potentially lead to the enhanced antigen presentation capacity of tumor cells, thereby allowing for more efficient priming of cytotoxic T-cells and improving therapeutic responses to ICI-based immunotherapy. Abbreviations: T-cell receptor (TCR); Granzyme B (GZMB), Perforin 1 (PRF1); Interferon γ (IFN γ).

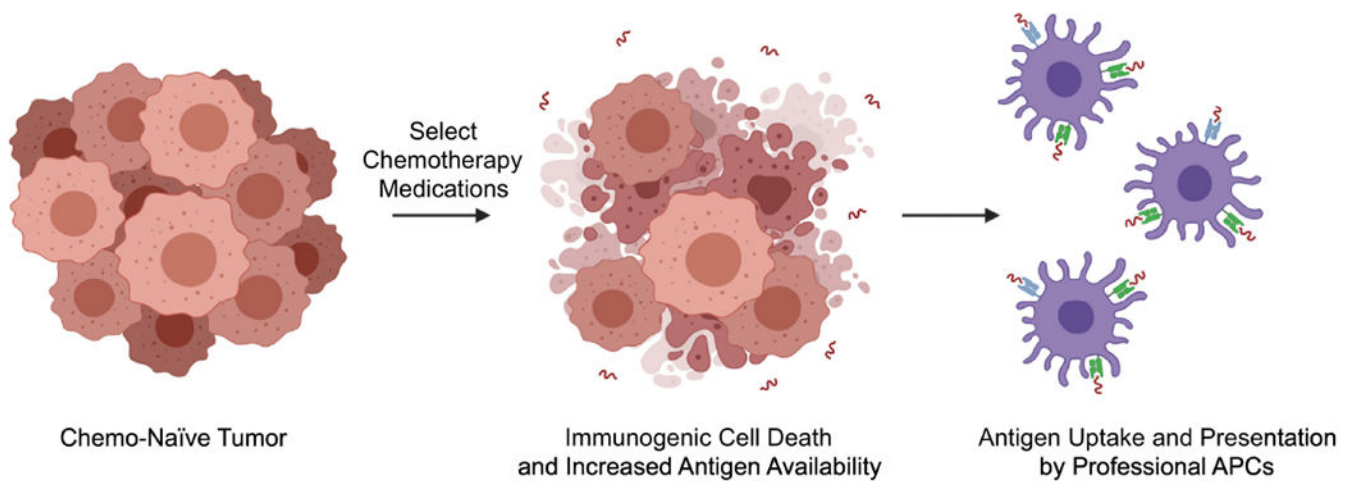


Figure 3. Chemotherapy-induced immunogenic cell death mobilizes tumor-antigen

In addition to enhancing HLA Class I-dependent antigen presentation, several chemotherapy medications can also promote immunogenic cell death. This process improves the availability of damage-associated molecular patterns (DAMPs) within the TME, thereby increasing the availability of tumor-antigen to professional antigen-presenting cells (APCs) and augmenting anti-tumor T-cell responses. The mechanisms through which chemotherapy induces immunogenic cell death are complex and, like more conventional antigen presentation, are best studied for platinum-based medications.

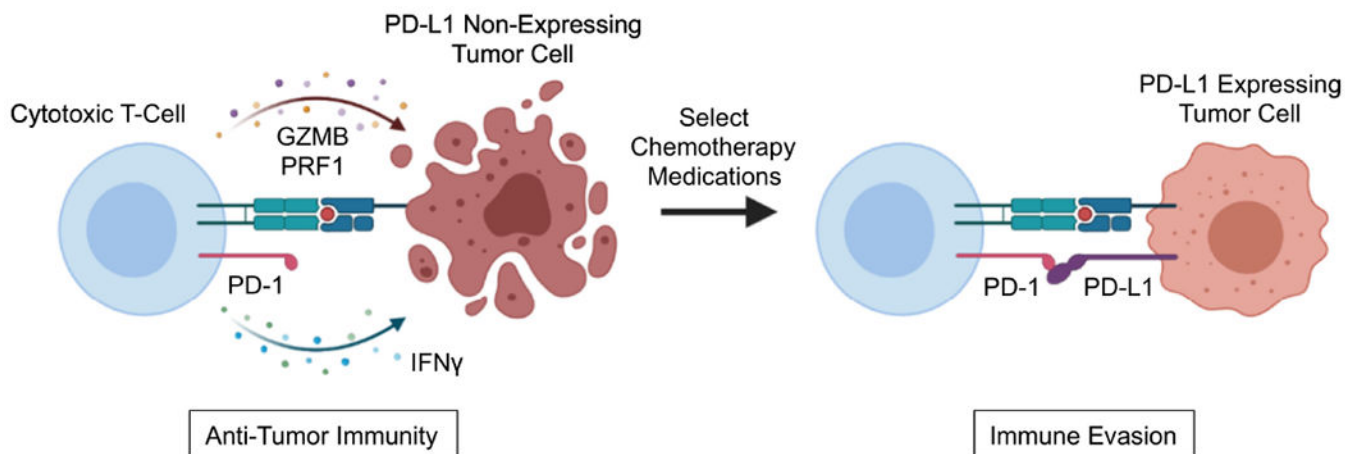


Figure 4. Chemotherapy-induced PD-L1 expression as a means of immune escape

Though chemotherapy can enhance tumor cell immunogenicity and potentiate immune-stimulating processes, such as antigen presentation, several chemotherapy agents can also enhance the expression of negative immune checkpoints, importantly PD-L1. In this context, PD-L1 can associate with the PD-1 receptor on effector T-cells, blunting anti-tumor immune responses and facilitating immune escape. This ligand/receptor interaction is neutralized by antibodies against PD-1 (e.g., pembrolizumab and nivolumab) or PD-L1 (e.g., atezolizumab, avelumab, and durvalumab), and several combinations of chemotherapy and anti-PD-1/PD-L1 antibodies are either in clinical use or under clinical evaluation. Abbreviations: Granzyme B (GZMB), Perforin 1 (PRF1); Interferon γ (IFN γ).

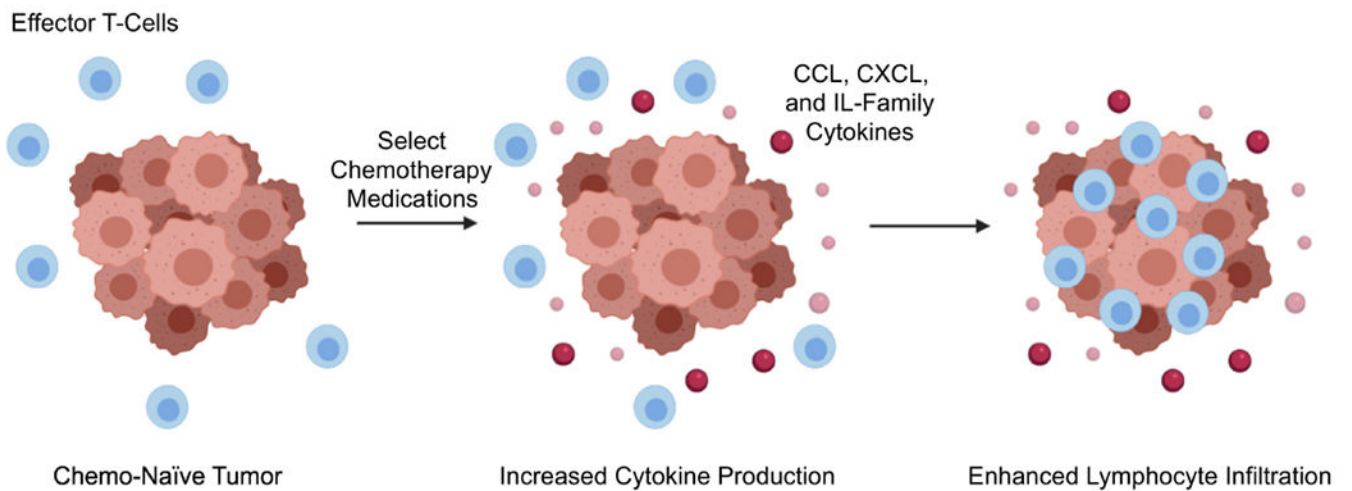


Figure 5. Chemotherapy enhances local cytokine synthesis and can facilitate lymphocyte trafficking into the tumor microenvironment

Several reports suggest that various chemotherapy medications can modulate tumor cytokine synthesis. For many cancers, chemotherapy can increase local levels of immune-stimulating cytokines/chemokines, thereby enhancing the recruitment of effector T-cells and promoting anti-tumor immunity. However, other reports suggest that chemotherapy often has contradictory roles regarding the local cytokine milieu and can also increase the release of several immune-suppressive signaling molecules. Hence, the success of future combination strategies may require the selective inhibition of chemotherapy-induced immune suppression in order to take full advantage of its immune-stimulating effects.

Table 1.

Select studies exploring the effects of platinum-based chemotherapy on tumor cell expression of antigen presenting molecules

Chemotherapy	Cancer Type	Effect on Antigen Presentation	Notes	Reference
Cisplatin	Breast	Increased MHC class I	-	(Wan, et al., 2012)
	Colon	Increased MHC class I	-	(Ohtsukasa, et al., 2003).
	Esophageal	Increased HLA-I	Combined with 5-FU	(Tsuchikawa, et al., 2012).
	Head & Neck	Increased MHC class I	-	(S. J. Park, et al., 2019).
	Head & Neck	Increased antigen presentation via MHC class I	-	(Tran, et al., 2017).
	Lung	Enhanced sensitivity to HLA-restricted cell death	Combined with Vinorelbine	(Gameiro, et al., 2012)
	Mesothelioma	Broadened the range of tumor antigens presented on MHC class I	-	(Jackaman, et al., 2012)
	Plasmacytoma	Increased MHC class I antigens	-	(Nio, et al., 2000).
Oxaliplatin	Colon	Increased mesothelin tumor antigens	-	(Galaine, et al., 2019)
	Colon	Increased antigen processing/presentation and MHC class I	-	(Y. Zhou, et al., 2021)
	Head & Neck	Increased MHC class I	-	(S. J. Park, et al., 2019).
	Liver	Increased HLA-I in tumors lacking an oncogenic <i>RAS</i> mutation	-	(Ledys, et al., 2018)
	Pancreas	Increased HLA-I	-	(Principe, et al., 2020)
	Prostate	Increased antigen processing/presentation and expression of MHC class I	-	(Y. Zhou, et al., 2021)
Carboplatin	Ovarian	Increased HLA-I	-	(Alagkiozidis, et al., 2011)

Table 2.

Select studies exploring the effects of non-platinum-based chemotherapy on tumor cell expression of antigen presenting molecules

Chemotherapy	Cancer Type	Effect on Antigen Presentation	Notes	Reference
Gemcitabine	Breast	Increased HLA-I	-	(W. M. Liu, et al., 2010).
	Breast	Increased HLA-I, Altered peptides eluted from HLA-I molecules	-	(Gravett, et al., 2018).
	Colon	Increased HLA-I	-	(W. M. Liu, et al., 2010).
	Colon	Increased HLA-I, Altered peptides eluted from HLA-I molecules	-	(Gravett, et al., 2018).
	Lung	Increased HLA-I	-	(W. M. Liu, et al., 2010).
	Lung	Increased HLA-I, Altered peptides eluted from HLA-I molecules	-	(Gravett, et al., 2018).
	Melanoma	Improved the cross-presentation efficiency of nuclear antigen	-	(Anyaegbu, et al., 2014)
	Pancreas	Increased MHC Class I in murine and HLA-I in human tumor cells	-	(Principe, et al., 2020).
Paclitaxel	Breast	Increased MHC Class I	-	Wan, et al., 2012)
	Pancreas	Increased HLA-I	-	(Principe, et al., 2020)
Mitoxantrone	Colon	Enhanced MHC class I	-	(Y. Zhou, et al., 2021)
	Prostate	Enhanced MHC class I	-	(Y. Zhou, et al., 2021)
5-FU	Pancreas	Increased HLA-I	-	(Principe, et al., 2020)
Etoposide	Breast	Increased MHC Class I	-	(Wan, et al., 2012)
Irinotecan	Pancreas	Increased HLA-I	-	(Principe, et al., 2020)
Topotecan	Breast	Increased HLA-I	-	(Wan, et al., 2012)
Vinblastine	Breast	Increased MHC Class I	-	(Wan, et al., 2012)

Table 3.

Landmark clinical trials supporting chemo-immunotherapy as a first-line treatment for lung cancer patients

Cancer Type	Chemotherapy	Immunotherapy	Phase	Notes	Ref
NSCLC	Pemetrexed and Platinum-based	Pembrolizumab	3	Metastatic, non-squamous, non <i>EGFR</i> - or <i>ALK</i> -Mutated	(Gandhi, et al., 2018)
	Carboplatin, and Paclitaxel/nab-Paclitaxel	Pembrolizumab	3	Squamous NSCLC only	(Paz-Ares, et al., 2018)
	Carboplatin and Pemetrexed	Camrelizumab	3	-	(C. Zhou, et al., 2021)
	Carboplatin and nab-Paclitaxel	Atezolizumab	3	-	(H. West, et al., 2019)
SCLC	Carboplatin and Etoposide	Atezolizumab	3	Extensive-stage disease	(Horn, et al., 2018)
	Etoposide and Platinum-Based	Durvalumab	3	Metastatic, non <i>EGFR</i> - or <i>ALK</i> -mutated	(Paz-Ares, et al., 2019)
	Carboplatin and nab-Paclitaxel	Atezolizumab	3	Included the VEGF-inhibiting antibody Bevacizumab	(Socinski, et al., 2018)

Abbreviations: Non-Small Cell Lung Cancer (NSCLC); Small Cell Lung Cancer (SCLC); Epidermal Growth Factor Receptor (EGFR); Anaplastic Lymphoma Kinase (ALK); Vascular Endothelial Growth Factor (VEGF).