EDITORIAL

Chemoimmunotherapy combinations: translating basic knowledge into clinical successes

While chemotherapeutic agents were long solely associated with immunosuppression, clinical data demonstrate that the combination of some chemotherapies with immunomodulators can be beneficial against cancer. Defining combinations featuring optimal anticancer activity along with minimal toxicity remains however a major challenge. Clinical evidence suggests that immune responses in patients treated with combination therapies are associated with progression-free survival. Progress in understanding the mechanisms responsible for anticancer immune responses following chemotherapy administration facilitated the translation of relevant chemoimmunotherapy combinations in the clinic.

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Almost 20 years ago Richard Lake and Bruce Robinson proposed that combining chemotherapy and immunotherapy could result in therapeutic benefits [1]. This assumption notably relied on preclinical results obtained with the chemotherapy gemcitabine and anti-CD40 antibody as an immunotherapy [2]. Chemotherapy or immunotherapy given alone failed to induce tumor control. However, treatment with gemcitabine followed by anti-CD40 drove tumor regression in up to 80% of the mice and led to the development of immunological memory [2]. While these results demonstrated potential synergistic effects between chemotherapy and immunomodulation, the clinical relevance of these observations for patients has long remained unexplored. Chemotherapy was indeed almost exclusively associated with immunosuppression because of its ability to target cells dividing rapidly, including the cells of the immune system. Because of this, the effectiveness of chemotherapies was primarily attributed to their ability to directly trigger cancer killing.

When researchers in the early 70 s interrogated the mechanisms underlying the anticancer efficacy of two anthracyclines, adriamycin and daunorubicin, some results seemed paradoxical. Daunorubicin featured enhanced activity against leukemic cells in vitro [3]. However, adriamycin featured better antileukemic activity than daunorubicin in vivo despite the absence of major differences in biodistribution of the two drugs [4]. In addition, the superior anticancer effect of adriamycin over daunorubicin was lost in mice devoid of immune responses due to previous irradiation [4], suggesting an involvement of immune responses in the anticancer activity of adriamycin. This contention was confirmed by multiple investigators over the next fifty years. While high-dose chemotherapy induces immunosuppression [5], relevant doses of chemotherapy can trigger immune responses against cancer.

Chemotherapies drive cancer cell death. This process results in the emission of mediators that can be sensed by the immune system. We have for instance reported that the release of danger signals such as High Mobility Group Box 1 (HMGB1) by dying tumor cells contributes to tumor immunogenicity [6]. HMGB1 binds to Toll-like receptor 4 (TLR4) on dendritic cells, ultimately leading the activation of T cell-mediated anticancer immune responses [6]. The molecular mechanisms explaining the abilities of chemotherapies to trigger an immunogenic form of tumor cell death (ICD) and their clinical relevance have been reviewed [7]. ICD is one of the ways by which chemotherapies can induce immune responses. Chemotherapies such as cyclophosphamide and 5-fluorouracil were notably shown to induce immune responses through their ability to eliminate regulatory T cells and myeloid derived suppressor cells [8], respectively. The mechanisms by which chemotherapies unleash anticancer immune responses against cancer have been discussed [9, 10].

While tumor cells contribute to immunosuppression in the tumor microenvironment (TME), activated immune cells can also paradoxically support the termination of anticancer immune responses. IFN-γ-producing CD8 T cells were shown to drive the expression of immunosuppressive factors such as indoleamine-2,3-dioxygenase (IDO) and Programmed death-ligand 1 (PD-L1) in the TME [11]. The ability of T cell-derived IFN-γ to induce PD-L1 expression in cancer cells was termed adaptive immune resistance [12]. Clinical observations in metastatic melanoma patients confirmed the relevance of this process by showing that patients responding to anti-PD-1 treatment featured enhanced proliferation of CD8 T cells in the TME [13]. Immune responses triggered by chemotherapies are rarely sufficient to drive tumor elimination, leading investigators to interrogate the reasons accounting for tumor resistance to immunogenic chemotherapies. We and others have interrogated the relevance of tumor adaptive immune resistance following chemotherapy administration. We showed that the release of IFN-γ drove the expression of PD-L1 on tumor cells, thereby leading to the dysfunction of PD-1-expressing T cells in tumors [14]. To restore productive anticancer immune responses, we combined anti-PD-1 treatment with chemotherapies. In two mouse models of colon cancer, we found that the addition of anti-PD-1 treatment to a combined administration of the two chemotherapies 5-fluorouracil and oxaliplatin markedly enhanced T cell effector responses and mouse survival [14]. Similar results were obtained by Pfirschke *et al.* who documented in lung, colon and fibrosarcoma cancer models that chemotherapies synergized with anti-PD-1 and anti-CTLA-4 therapy [15]. Overall, preclinical investigations demonstrated the relevance of combined treatment of chemotherapy with immune checkpoint inhibition for durable cancer control (Fig. 1).

The clinical relevance of combination of chemotherapies and immunomodulation was recently explored in patients bearing

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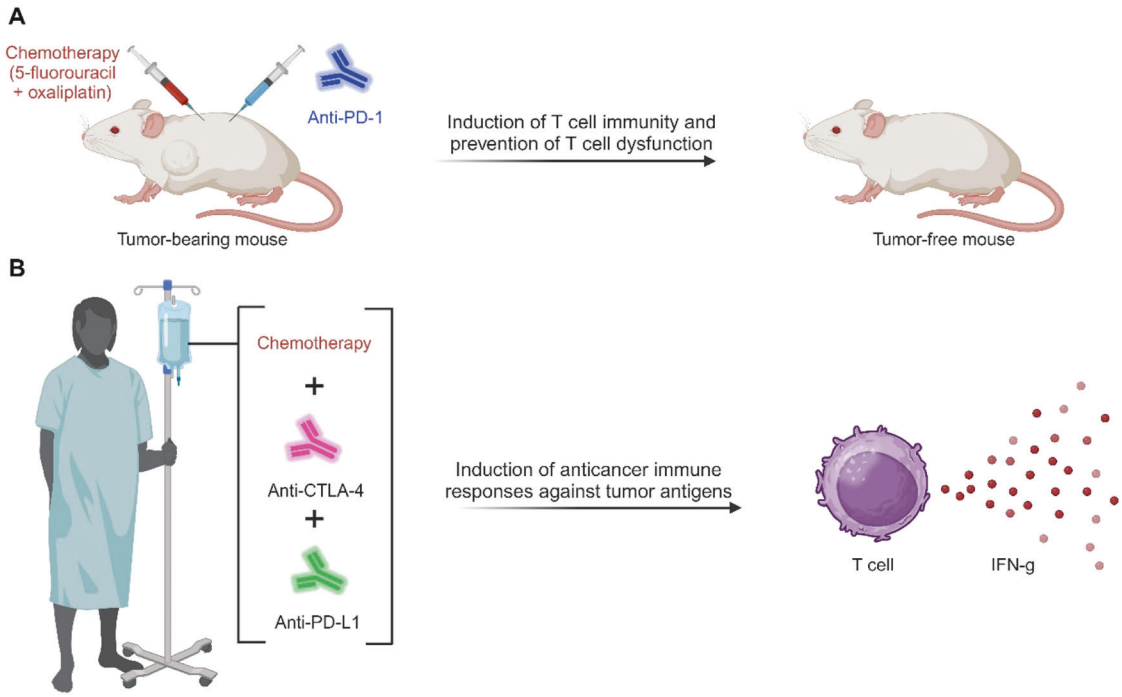

Fig. 1 Translation of chemoimmunotherapy into the clinical practice. A Combination of 5-fluorouracil and oxaliplatin in mice along with anti-PD-1 treatment prevents tumor-induced T cell dysfunction and extends mouse survival [14]. **B** The addition of anti-PD-1 and anti-CTLA-4 antibodies to MSS colon cancer patients receiving chemotherapy triggers anticancer immune responses [16].

MicroSatellite Stable (MSS) colon cancer. Building on early investigations described above suggesting beneficial effects of combining 5-fluorouracil, oxaliplatin, and immunomodulation [14], Thibaudin et al. tested in a phase Ib/II clinical trial the safety and efficacy of a combination of chemotherapy, with durvalumab, an anti-PD-L1 antibody and tremelimumab, an anti-CTLA-4 antibody administered to patients bearing metastatic colon cancer [16]. Results from 48 patients revealed a median progression-free survival (PFS) of 8.2 months, which is superior to the expected median PFS of 5 to 6 months with chemotherapy alone. Importantly, 6 patients achieved a complete response, indicating that chemo-immunotherapy combinations are clinically effective [16]. Analysis of immune responses against the tumor antigens telomerase and NY-ESO1 revealed that the combination treatment induced enhanced T cell responses against these tumor antigens after one treatment cycle [16]. Importantly, increased T cell responses in this setting were associated with longer PFS. While the combined treatment triggered adverse events in some of the patients leading to treatment discontinuation, these results altogether indicate that combination therapies can harness anticancer immune responses in metastatic MSS colon cancer patients [16].

The example above is one of the successful implementations of chemotherapy and immunomodulation combinations in the clinic (reviewed in [17]). These results are notably in line with recent findings documented in advanced oesophageal cancer. Immunomodulation using anti-PD-1 antibodies administered with chemotherapy improves the overall survival of oesophageal squamous cell carcinoma (OSCC) patients as compared to chemotherapy alone [18]. A recent phase 3 clinical trial interrogated the relevance of anti-PD-1 combined with different chemotherapy associations, oxaliplatin or cisplatin plus capecitabine or fluorouracil or paclitaxel, compared to chemotherapies alone as first-line treatment for OSCC. Results revealed that the beneficial therapeutic effects of the combination were not restricted to the use of the cisplatin and fluorouracil combination, but also to multiple chemotherapy combinations tested by the investigators [19]. These results not only provide additional therapeutic options for patients suffering from oesophageal cancer, but also suggest that the ability to administer relevant clinically chemoimmunotherapy combinations is a concept that is broadly applicable (Fig. 1). Further investigations into the genetic and immunological biomarkers associated with the success of chemoimmunotherapy combinations will ultimately ease further their clinical implementation.

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