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Do immune checkpoint inhibitors increase sensitivity to salvage chemotherapy?

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“there is a lack of cross resistance between the two classes of treatment and response to chemotherapy is maintained independently of previous exposure to ICI. This retrospective study also showed that ICI exposure could enhance tumor sensitivity to conventional chemotherapy.”

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Immune checkpoint inhibitors (ICI) are profoundly changing the treatment of solid and hematologic malignancies and becoming an integral part of the management of cancer patients. These agents led to distinguished durable response in approximately 20% of patients when given a second or subsequent line of therapy with a manageable safety profile [1]. We thought that prior treatment with chemotherapy can enhance tumor sensitivity to PD-1/PD-L1 inhibitors. It has been reported that chemotherapeutic agents could induce immune-reactive effects such as cross-presentation of tumor antigens or MHC class I molecules and reducing T regulatory cells or myeloid derived suppressor cells which increases the accumulation of helper T cell at the tumor site [2–4]. Recently, Peng *et al.* showed that chemotherapy enhances PD-L1 overexpression via the NF- κ B and creates an immunosuppressive tumor microenvironment in ovarian cancer [5]. In fact, the high expression of PD-L1 and the decreased T regulatory cells or myeloid derived suppressor cells was associated with better response to ICI [6]. However, do ICIs increase sensitivity to salvage chemotherapy?

What is the rationale?

Some reports in the literature showed that response to chemotherapy can be increased in patients exposed to vaccine-based immunotherapy in different types of cancer. For example, Antonia *et al.* reported an objective clinical response of 61.9% to chemotherapy after vaccination with dendritic cells transduced with the full-length wild-type p53 gene in patients with advanced stage small-cell lung cancer [7]. The treatment with a cytochrome P450 1B1 vaccine was associated with high response to salvage chemotherapy in patients who developed immunity to CYP1B1 [8]. In hormone refractory prostate cancer, docetaxel showed a significantly longer time to progression in patients immunized with recombinant viral vectors containing the PSA and B7.1 genes compared with patients who received docetaxel alone in a randomized Phase II study [9]. Similarly, Wheeler *et al.* reported that patients who received chemotherapy after an autologous tumor-pulsed dendritic cell vaccine exhibited significantly longer time to tumor recurrence and survival advantage than patients treated with chemotherapy alone in patients with glioblastoma [10]. These reports suggest that immunotherapy could sensitize tumor cells and enhance the effect of chemotherapy.

What about immune checkpoint?

Concerning ICI, it has been demonstrated that inhibition of PD-1 on CD8⁺-tumor-infiltrating lymphocytes using anti-PD-1 can restore cytokine secretion and T cell proliferation [11] rising the hypothesis that immune checkpoint inhibition can activate the immune system, change the natural history of the disease and the microenvironment rendering tumor cells more sensitive to chemotherapy.

Recently, Leger *et al.* presented in abstract form a response rate of 27% to salvage chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) who had progressed on checkpoint inhibitor. The odds ratio for achieving partial response was 0.30. Docetaxel was the most frequently administered chemotherapy in these patients (62%) [12]. Furthermore, Schvartsman *et al.* reported the objective response rate (ORR) to single-agent chemotherapy after exposure to PD-1 or PD-L1 inhibitors in patients with advanced NSCLC at MD Anderson Cancer Center. In his cohort of 28 patients, the confirmed ORR to single-agent chemotherapy was 29%, with another three patients who presented unconfirmed partial responses raising the ORR to 39%. The median progression-free survival was 4.7 months and the overall survival was 9.0 months. Docetaxel was the chemotherapy most frequently used after progression on ICI. However, all patients in Schvartsman's cohort did not respond to immunotherapy (ORR: 0%) and four patients had EGFR-mutation known to increase sensitivity to conventional chemotherapy [13]. It seems that the ORR to salvage chemotherapy is higher than response reported with second-line docetaxel in advanced NSCLC. Overall there are no data showing that patients having durable response on immunotherapy will have the same or a more favorable response rate than patients with rapidly progressive disease after ICI. The question remains: do patients who rapidly progress after beginning of immunotherapy have more response to conventional chemotherapy?

Does sequencing of chemotherapy & ICI maximize the outcome in cancer patients?

Emerging data showed an excellent response rate to chemotherapy after exposure to first-line ICI in patients with metastatic urothelial carcinoma (64%) [14]. Szabados *et al.* compared the response rate to salvage chemotherapy following ICI exposure of two cohorts of patients (total 28 patients): the first cohort concerned patients who received ICI in first-line setting followed by chemotherapy and the second one consisted on patients who received chemotherapy followed by ICI then chemotherapy after progression. Information concerning ICI in this study was not given since patients were included in clinical trials. The response rate in the first cohort was 64% comparable to the 50% of response to standard platinum-based chemotherapy in the first-line setting [15]. The response rate to salvage chemotherapy in the second cohort was 21% in third line which is concordant with the results in patients who progressed on first line without prior exposure to ICI [16]. The authors concluded that there is a lack of cross resistance between the two classes of treatment and response to chemotherapy is maintained independently of previous exposure to ICI. This retrospective study also showed that ICI exposure could enhance tumor sensitivity to conventional chemotherapy.

Future perspective

All the above showed that previous exposure to PD-1/PD-L1 inhibitors could increase sensitivity to salvage chemotherapy in patients who progressed on ICI. However, this is based on retrospective findings reported on small populations and in much selected groups of patients. More investigations should be done to confirm if patients who initially responded to immunotherapy had also an important response rate to salvage chemotherapy and if a specific sequencing of standard chemotherapy and PD-1/PD-L1 inhibitors could improve patients' survival. Ongoing randomized trials may validate these findings.

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