Editorial

Would the skyrocketed advances of immune checkpoint inhibitors over chemotherapy be stumbled by the safety issues?

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Immune checkpoint inhibitors (ICIs) have inaugurated a new era in the treatment of advanced malignancies. It is not only associated with higher progression-free survival and overall-survival but also a durable response that reached to 10 years in certain subsets of patients (1). This superiority over conventional chemotherapy regimens guaranteed an approval for ICIs in second and even first lines in treatment of non-small cell lung cancer (NSCLC), melanoma and renal cell carcinoma. Of those molecularly defined immune targeting, PD-1 and PD-L1 pathways are influential in suppressing effector immune response against tumor. That's why anti-PD-1 and PD-L1 monoclonal antibodies (mAbs) could induce sustainable anti-tumor immune response. Unfortunately, this immune system manipulation may lead to emergence of autoimmune manifestations, usually reported as immune-related adverse effects.

The promising results of anti-PD-1/PD-L1 mAbs in many advanced tumors introduced a new paradigm in cancer drug approval based on certain biomarkers irrespective of tissue/organ of origin. Pembrolizumab was the first to get "tumor-agnostic" approval from US FDA (2). This means that anti-PD-1/PD-L1 will be available option to use in many tumor types that were conventionally managed with certain lines of chemotherapy. Awareness to the different safety profile between these chemotherapy regimens and ICIs is of utmost importance as direct head-to-head comparison of safety data may not be available from clinical trials.

Nishijima *et al*. published a meta-analysis in *the Oncologist* addressing the issue of safety of PD-1/PDL-1 inhibitors compared to chemotherapy (3). The analysis included 7 randomized trials all but one was open label recruiting 2,090 patients receiving PD-1/PD-L1 mAb versus 1,360 receiving chemotherapy. The authors categorized the analyzed adverse effects into three main groups with distinct clinical relevance.

First category included conventional treatment-related symptoms entailing the eight commonly reported symptoms across the seven trials. Fatigue, anorexia, nausea, constipation, diarrhea and sensory neuropathy were associated with significant lower relative risk in anti-PD-1/PD-L1 group. Moreover, only high-grade fatigue, diarrhea and sensory neuropathy were associated with significant lower relative risk with PD-1/PD-L1 inhibitors. Other all grade and high-grade symptoms showed no statistically significant differences between the two groups. These results are apparently in contrary to previous meta-analysis that showed an increase risk of GI toxicities with ICIs (4). This can be explained in part that this meta-analysis included an anti-CTLA-4 and the comparison arm was heterogenous including both chemotherapy and placebo controls. Moreover, the subgroup analysis showed an increase in the risk of diarrhea with ipilimumab-based regimen and this did not hold true for nivolumab, an anti-PD-1 mAb. Diarrhea in particular warrants further analysis based on individual patients' data as it might underlie autoimmune GI affection but it is still reassuring that incidence of all and high grade-diarrhea were low among PD-1/PD-L1 inhibitors group.

Second category included all grade and high grade hematologic toxicities. A significantly lower relative risk was found in patients of PD-1/PD-L1 inhibitor group for hematological toxicity compared to control regimens. It is worth noting that the most commonly compared chemotherapy regimen was docetaxel (in four trials of NSCLC).

Third category is the immune-related AEs; and -as

expected- they showed a higher risk with PD-1/PD-L1 inhibitors including dermatologic, endocrinopathies, and pneumonitis. Interestingly high-grade AEs in such category showed non-significant difference between the two groups except for incidence of high-grade pneumonitis with PD-1/PD-L1 inhibitors compared with chemotherapy (1.3% versus 0.6%; RR 3.21, P=0.01). This is supported with results of our meta-analysis of eleven trials that found an increased risk of pneumonitis with ICIs in comparison to chemotherapy or placebo (5). Again, this meta-analysis included anti-CTLA-4.

An interesting point discussed by authors is the patients' reported outcomes (that was included in design of two of the analyzed trials and many other ongoing trials). Patients who received PD-1 inhibitors reported better global health status quality-of-life score. Another intriguing point is that the age and performance status, the major two determinants in chemotherapy choice and clinical decision making, did not demonstrate any clear difference in efficacy and toxicity outcomes rendering the PD-1/PD-L1 inhibitors potential choice for older and frail patients.

We are concerned about generalizing the results of this meta-analysis as the comparison arm in most occasions was single agent docetaxel. Although the authors performed subgroup analysis based on type of chemotherapy regimen (docetaxel versus others), we cannot come to an unequivocal conclusion that PD-1/PD-L1 inhibitors are more tolerable and safe than conventional chemotherapeutic regimens. Further focused analysis of certain toxicity endpoints is still required, pneumonitis is a striking example in such regard (6). For instance, a recent meta-analysis revealed that the risk of pneumonitis was lower in patients who received prior chemotherapy in comparison with treatment-naïve group (7) reflecting that the relationship between ICIs and chemotherapy is intermingled at many points and the patients with advanced cancer should be counselled on the risks and benefits of both approaches.

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