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Can we do without chemotherapy? A perspective on the combinations nivolumab-chemotherapy and nivolumab–ipilimumab in metastatic gastric and esophageal cancer

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Introduction

Exciting new studies have changed the therapeutic landscape of gastric and esophageal cancer. Adding the programmed cell death protein 1 (PD-1) inhibitor nivolumab to frontline platinum and fluoropyrimidine-based chemotherapy improves outcome in both gastroesophageal adenocarcinomas (GEA)[1,2] and esophageal squamous cell carcinoma (ESCC)[3,4] with an acceptable toxicity profile. For GEA, this was most clearly observed in patient with a programmed death ligand-1 (PD-L1) combined positivity score (CPS) of $\geqslant 5$ within the Checkmate (CM) 649 study, for ESCC this was mostly true for patients with tumoral PD-L1 expression ≥ 1 (CM648 study) and CPS score $\geqslant 10$ (KEYNOTE-590 study).[4]

Interestingly, both the CM648 and CM649 studies also tested the chemotherapy-free treatment regimen consisting of ipilimumab/nivolumab combination treatment. In GEAs, the ipilimumab/nivolumab treatment arm did not improve outcome and was even closed early, owing to increased rate of adverse events and early deaths. However, in the small subgroup of cancer with microsatellite instability (MSI), the ipilimumab/nivolumab treatment was associated with a longer overall survival and response rate compared to chemotherapy alone. For ESCC, frontline combination immunotherapy showed much better outcome compared to chemotherapy alone for the entire group of ESCC with tumoral PD-L1 expression ≥ 1. Thereby, for ESCC, both immunotherapy options, nivolumab/chemotherapy and combination immunotherapy, are currently available as first-line treatment. As the CM studies were not designed to make a direct comparison between the chemotherapy/nivolumab and ipilimumab/nivolumab arms, no assurance can be provided about which treatment arm is better. Therefore, the question remains: *can we do without chemotherapy?*

Crossing of survival curves

Although a direct comparison between chemotherapy/nivolumab and ipilimumab/nivolumab arms cannot be made, for ESCC comparable improvement in overall survival was seen when the treatment arms were compared to chemotherapy alone within the CM648 study.[3] The nivolumab/chemotherapy arm was associated with a longer median overall survival of 15.4 months compared to chemotherapy alone [9.1 months, hazard ratio (HR): 0.54, confidence interval (CI): 0.37–0.80] in the group of patients with tumoral PD-L1 expression $\geqslant 1$. The same accounts for the combination immunotherapy arm which had a higher median overall survival of 13.7 months compared to the chemotherapy arm (HR: 0.64, CI: 0.46–0.90). However, the pattern of the overall survival curve was different between the nivolumab/chemotherapy and ipilimumab/nivolumab arm. While the nivolumab/chemotherapy and chemotherapy

arm start to separate in the first months after start, for the ipilimumab/nivolumab and chemotherapy arms survival curves first cross before they diverge much later.

Late divergence of survivals curves is commonly observed in immune-oncology trials and is often prescribed to a delayed activation of an anti-tumor T-cell response compared to chemotherapy that regularly induces a direct cytotoxic effect. However, an alternative explanation is that immunotherapy is most effective in slow progressing cancers that are already kept in check by the immune system and only need an extra push by checkpoint inhibition (recently reviewed by Thorén *et al.*[5]).

Independent of the mechanisms of delayed divergence of the survival lines, the findings of the CM649 trial that for PD-L1+ GEAs the ipilimumab/nivolumab combination was inferior to chemotherapy in the first 12 months of treatment and that 55% of patients already passed away before the survival curves crossed in favor of combination immunotherapy.[1,2] For PD-L1+ ESCCs, the ipilimumab/nivolumab combination was inferior to chemotherapy in the first 6.5 months before the curves crossed and diverged.[3] Together, these studies show that selecting patients based on PD-L1 expression alone does not overcome the risk of rapid progression or lack of response to immunotherapy combination treatment. Combining checkpoint inhibitors with chemotherapy can likely mitigate the detrimental effect of fast progressive disease in the first months.

It should be noted that when combining a checkpoint inhibitor with chemotherapy, the question whether a specific combination of cytotoxic agents should be preferred, is still unanswered. In CM649, the chemotherapy backbone was oxaliplatin combined with capecitabine or 5-fluorouracil, while in CM648 cisplatin was combined with 5-fluorouracil. In a network meta-analysis of randomized studies in gastroesophageal adenocarcinoma (GEA), it has been established that in view of efficacy and toxicity, fluoropyrimidine containing doublets with oxaliplatin, irinotecan, or taxanes are preferred as first-line treatment for GEA compared with cisplatin-containing doublets and anthracycline triplets.[6] Unfortunately, randomized studies comparing cytotoxic regimens for the first-line treatment of ESCC are lacking, and usually the GEA treatment guidelines are followed.[7] Several *in vitro* and *in vivo* studies have suggested that the tumor immune microenvironment may be modulated by different chemo(radio)therapy or targeted agents in a specific tumor type, thus potentially influencing the efficacy checkpoint inhibitors including nivolumab.[8] However, the effect of specific cytotoxic agents on the immune microenvironment and its influence on response to checkpoint inhibitors in a clinical setting is largely unknown. The proinflammatory and anti-inflammatory effects of cytotoxic agents, which have been identified thus far, need to be established in a cancer-specific and compound-specific manner.

Can we identify clinical subgroups that specifically do or do not benefit from a chemotherapy-free combination immunotherapy regimen?

Given the side effects of cytotoxic treatment regimens in general, and for metastatic gastric and esophageal cancer in particular,[9] chemotherapy-free regimen for patients with metastatic disease is an appealing approach. For some patients, a treatment regimen with lower chances of survival may still be their treatment of choice if in this way they can avoid treatment-related adverse events. Although generally speaking, combination immunotherapy indeed comes with less side effects than chemotherapy or chemotherapy combined with checkpoint inhibition, combination immunotherapy is not without side effects. For example, in CM649, treatment-related adverse events leading to discontinuation of treatment still occurred in more than 20% of patients treated with nivolumab plus ipilimumab (38% and 25% of patients in the nivolumab-plus-chemotherapy *versus* chemotherapy groups, respectively, and in 22% and 26% of patients in the nivolumab-plus-ipilimumab *versus* chemotherapy groups).[1,2] Clearly, the spectrum of side effects differs, with, for example, more neutropenia in the group of patients treated with chemotherapy with or without nivolumab, while immune-related events were more common in the group of patients treated with the two checkpoint inhibitors. Thus, a careful discussion with patients on the pros and cons of different treatment options, both in terms of survival and in terms of side effects is of utmost importance. Web-based tools and training programs that are currently in development can aid physicians in this complex task.[10]

Given the lower incidence of side effects in the chemotherapy-free combination immunotherapy

regimen of nivolumab and ipilimumab, healthcare providers may be tempted to advice this treatment to patients with a poor performance status. It should be noted, however, that in the CM studies patients were only included if they had a good performance status (ECOG PS 0-1) and, in principle, were physically sufficiently fit to undergo cytotoxic treatment. In fact, in CM648, which reports subgroup analyses for overall survival, patients with ECOG PS 0 may derive more benefit from combination treatment with checkpoint inhibitors only compared to chemotherapy, than patients with ECOG 1 (HR: 0.73; CI: 0.55–0.98 and HR: 0.81; CI: 0.63–1.03, respectively). This resonates a protocol-specified subgroup analysis in KEYNOTE-061, where a significant overall survival benefit in favor of pembrolizumab over paclitaxel was seen in patients with ECOG PS of 0.[11] However, this trend was not observed in the KEYNOTE-062 study, a phase III trial in which first-line pembrolizumab monotherapy was compared to pembrolizumab plus chemotherapy *versus* chemotherapy alone in patients with advanced gastric/gastroesophageal junction.[12]

Following the hypothesis that immunotherapy is most effective in slow progressing cancers that are already kept in check by the immune system,[5] one could argue that in patients with limited tumor burden double immunotherapy could be the treatment of choice if patients want to avoid chemotherapy toxicity. In CM648, patients with maximally one organ with metastases – which could be regarded a proxy for limited disease – seemed to derive slightly more benefit from combination treatment with checkpoint inhibitors only compared to chemotherapy, than patients with two or more organs involved (HR: 0.76; CI: 0.58–1.00 and HR: 0.81; CI: 0.63–1.05). Please note that for these subgroup analyses no survival curves have been shown and it is unclear whether crossing of survival curves is an issue in these subgroups.

Based on previous findings that the magnitude of benefit of treatment with checkpoint inhibitors is sex dependent,[13] the subgroup analysis of males *versus* females in CM 648 is worth noting. Male patients could derive survival benefit from combination treatment with checkpoint inhibitors only compared to chemotherapy, but females did not (HR: 0.70; CI: 0.57–0.86 and HR: 1.36; CI: 0.85–2.20, respectively). Based on this result, females should be advised to have chemotherapy added to their treatment regimen. This gender difference was not for adenocarcinomas within the KEYNOTE-061, KEYNOTE-062, or CM 649 and might therefore be histological subtype specific.

Novel biomarkers for treatment selection

So far, the best biomarker for response to checkpoint inhibitors in gastric and esophageal cancer is PD-L1 expression. Besides CM648 and CM649, KEYNOTE-059[14] and KEYNOTE-061[11] also identified that patients with PD-L1 expression (CPS $\geqslant$ 1) benefit most from checkpoint inhibitors. Nevertheless, PD-L1 expression was not sufficient to select a group of patients that would actually benefit from the chemotherapy-free combination regimen nivolumab–ipilimumab rather than the combination of nivolumab with chemotherapy.

Given the generally good response of MSI-high tumor to checkpoint inhibitors, MSI status might be the most obvious biomarker to select patients for a chemotherapy-free combination immunotherapy regimen. In fact, according to the TCGA classifications, the MSI group represents a distinct subset of gastric cancers, next to the EBV group, genomically stable group and the chromosomal instable group. In CM649, patients with MSI-high tumors clearly benefited from any of checkpoint inhibition regimens compared to the chemotherapy-only regimen. However, the CIs of the HRs for survival of nivolumab plus chemotherapy *versus* chemotherapy and nivolumab plus ipilimumab *versus* chemotherapy were largely similar (unstratified HR: 0.38, 95% CI: 0.17–0.84 and unstratified HR: 0.28; 95% CI: 0.08–0.92, respectively).[1]

Thus far, other biomarkers have not been investigated in the CM649 and CM648 studies. Based on high response rates observed in a phase II trial in a Korean cohort of patients, Epstein-Barr virus (EBV) positivity might be the next most promising biomarker to explore.[15] However, in the KEYNOTE-061 study,[16] 13% of patients with EBV+ gastric cancers (2/15) responded to pembrolizumab compared to and 15% (2/13) in the paclitaxel arm which was in agreement with finding of the KEYNOTE-059[14] in which none of the 5 EBV+ gastric cancers responded. Thereby, evidence to support the role of EBV as biomarker for response to immunotherapy is mostly anecdotal[17] and needs further investigation in first line setting.

Alternative biomarkers for PD-1 inhibitors are currently explored among which a high tumor mutational burden (TMB).[16] A post-hoc analyses of the KEYNOTE-061 study showed that TMB-H assessed by whole exome sequencing did correlate with a higher response rate, a longer progression-free survival and overall survival which was specific for the pembrolizumab group and not observed in the paclitaxel arm. Interestingly, this association was still present after exclusion of MSI cancers, something that was not observed for the KEYNOTE-062 study in which the association between TMB-H (FoundationOne CDx assay, cutoff of 10 mut/Mb) and an improved clinical outcome in the pembrolizumab treatment arms disappeared after exclusion of MSI cases.[18] In a recent biomarker analyses of the CM649 presented at the AACR 2022,[19] however, the association between TMB-H and benefit of immunotherapy was also observed in the MSS group of cancers. The magnitude of benefit of nivolumab + chemotherapy *versus* chemotherapy alone for the entire group was greater in patients with PD-L1 CPS $\geq$ 5 and TMB-H cancer (HR: 0.44) compared to the PD-L1 CPS $\geq$ 5 and TMB-L group of patients (HR: 0.75). Interestingly, also a low epithelial–mesenchymal transition signature and a low angiogenesis signature were associated with greater overall survival benefit of the nivolumab + chemotherapy combination. However, as benefit of nivolumab was observed in all patients with PD-L1 CPS $\geq$ 5, the clinical utility of these biomarkers is not entirely clear.

Combination immunotherapy: moving the field further

From an immunological point of view, the combination of ipilimumab and nivolumab was a rational choice, as they activate the antitumor immune response differently. Ipilimumab is a fully humanized monoclonal antibody against Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4 becomes upregulated in response to T-cell activation and competes with CD28 to bind with CD80 and CD86 on antigen-presenting cells to downregulate a T-cell response; a homeostatic mechanism to prevent unwanted auto-immunity against self antigens.[20] Blocking CTLA-4 prolongs T-cell activation and restores T-cell proliferation and can enhance an antitumor immune response in immunogenic cancers. Nivolumab is a fully humanized monoclonal antibody against PD-1. By its interaction with PD-1, nivolumab selectively blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2 to prevent downregulation of the antitumor immune response induced by the expression of the ligands on tumor cells and antigen-presenting cells.

Despite the theoretical advantage of the combination of ipilimumab and nivolumab, it is still unclear whether the addition of ipilimumab to nivolumab expands the spectrum of GEA and ESCC patients that respond to immunotherapy, as nivolumab monotherapy was not tested within the CM648 and CM649 studies. However, studies have shown that the tumor immune microenvironment of ESCCs is dominated by exhausted T cells, but also other immune suppressive cell populations such as regulatory T cells, myeloid-derived suppressor cells and M2-type, suppressive macrophages.[21] Furthermore, in ESCC PD-L1 is often co-expressed with other immune inhibitory receptor such as *T-cell immunoglobulin and mucin-domain-containing-3* (TIM3) and TIGIT,[22] which is associated with a poor prognosis. The effectivity of TIM-3 or TIGIT targeting agents with and without PD-L1 targeting agents is under active investigation (SKYSCRAPER-07, NCT04543617).

For GEA, the immune microenvironment is often T cell excluded while macrophages do populate the intratumoral area.[23] Furthermore, esophageal adenocarcinomas often overexpress PD-L2 as a result of IL4 and IL13 expression in a chronically inflamed microenvironment that also harbors immune suppressive M2 macrophages.[24] T-cell exclusion and presence of immune suppressive myeloid population is a central feature of tumors that do not respond to checkpoint inhibition.[25] Targeting myeloid cell population together with T cells might be a more successful approach.

In conclusion, the addition of immunotherapy to first-line treatment in esophageal and gastric cancers has significantly changed the therapeutic landscape of these diseases. Although combination immunotherapy improves outcome compared to chemotherapy alone in ESCCs, choosing a chemotherapy-free treatment regime should be done with cautions as it takes months before combination immunotherapy outperforms chemotherapy. Biomarkers to support clinical decision-making are highly needed, which is still a topic of active investigation.

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