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Spotlight

Two types of biomarker-dependent chemo-immunotherapy for pancreatic cancer?

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Padron et al.[1] studied the combination of chemotherapy (gemcitabine and nab-paclitaxel) with either an anti-PD1 (nivolumab) or an anti-CD40 (sotigalimab) antibody in metastatic pancreatic cancer. They showed clinical benefit in individuals with unique biomarkers for each treatment combination

Pancreatic ductal adeno carcinoma (PDAC) is considered to be one of the deadliest of all cancers. By the time the diagnosis is made, locally advanced or metastatic PDAC has often already abolished the possibility of curative treatment by surgery. This is the result of a lack of symptoms of earlier disease associated with metastasis to the liver and elsewhere. The standard treatment for advanced inoperable PDAC is chemotherapy with Folfirinox (fluorouracil, leucovorin, irinotecan, and oxaliplatin) or with gemcitabine and nab-paclitaxel. Although this treatment can reduce disease burden and provide temporary relief of symptoms, very few individuals survive beyond 5 years.[2] While immune checkpoint inhibition (ICI) treatment has proven to be effective in individuals with various types of advanced cancer associated with many mutations, such as melanomas and non-small cell lung cancer and cancers in individuals with mismatch repair deficiencies,[3,4] ICI treatment has been notoriously ineffective in people with PDAC.[5]

Recently published in *Nature Medicine*, the paper by L.J. Padrón et al.[1] provides a detailed account of a heroic effort to change this situation. In this randomized phase 2 study of 105 individuals with first-line metastatic PDAC, individuals were randomized into 3 groups. The first group received chemotherapy (gemcitabine and nab-paclitaxel) in combination with the ICI drug nivolumab (monoclonal antibody blocking the inhibitory PD-1 receptor on T cells). The second group received the same chemotherapy in combination with sotigalimab, an agonistic monoclonal antibody against the master switch molecule CD40, expressed on B cells and dendritic cells (DCs). Finally, a third group was given the same chemotherapy in combination with both nivolumab and sotigalimab. The investigators decided to not randomize for recruitment to a control group treated only with the standard of care chemotherapy, because they feared that this would drastically reduce the attractiveness of the trial for individuals. It was recognized, however, that any improvements in comparison with the now historical control of chemotherapy alone would have to be evaluated in a randomized phase 3 trial.[1] The choice of these treatment groups is well argued by the investigators.

PDAC tissues contain mutations creating mutation-derived neo-antigens, including Kras-driver mutations eliciting T cell responses,[6,7] making ICI treatment in combination with chemotherapy a good choice. PD-1 blocking acts by inhibiting the interaction of PD-1 on T cells with PD-L1 on intra-tumoral DCs and cancer cells. The chemotherapy component contributes by tumor debulking, by depleting myeloid suppressor cells, by inducing antigen release for uptake by T cell response initiating DCs, and finally by causing immunogenic cell death that activates DCs. CD40 agonist antibody is one of the most powerful activators of B cells and DCs and therefore acts through a mechanism completely different from anti-PD-1. Anti-CD40 agonist antibody had shown promising activity in preclinical mouse models of PDAC[8] and in a phase I clinical trial in individuals with locally advanced or metastatic PDAC.[9]

The primary endpoint in the study was patient survival (overall survival, OS) 1 year after initiation of each therapy.[1] The assumption was that 35% of individuals would survive at 1 year with this type of chemotherapy alone.[9] The primary endpoint was only met for individuals who had been treated with nivolumab and chemotherapy (OS 57.7%, $p = 0.006$ compared to the historical 1-year OS of 35%, $n = 34$) but was not met for the sotigalimab/chemotherapy combination (OS 48.1%, $p = 0.062$, $n = 36$) or the sotigalimab/nivolumab/chemo combination (OS 41.3%, $p = 0.223$, $n = 35$).[1] On the other hand, there was no statistically significant difference between the nivolumab/chemotherapy and sotigalimab/chemotherapy groups. Survival after nivolumab/chemotherapy correlated with a less-suppressive tumor microenvironment and higher numbers of activated, antigen-experienced circulating T cells at baseline. In particular, T follicular helper cells ($CD4^+PD\text{-}1^+CXCR5^+$) were associated with longer survival and had the highest predictive value of the strongest circulating biomarkers in the nivolumab/chemotherapy arm. These cells had high expression of TCF-1, CCR7, and ICOS.[1] High frequencies of these cells late on treatment were most differentiating between individuals with OS > 1 year and <1 year. Individuals with longer survival after the sotigalimab/chemotherapy treatment, in contrast to those who survived longer following nivolumab/chemotherapy, had higher pre-treatment frequencies of circulating DCs and B cells and DC phenotypic changes on treatment.[1] The OS in individuals receiving all three treatment modalities

tended to be worse than in the nivolumab/chemotherapy and situgalimab/chemotherapy combination groups, and preliminary evidence of hyperstimulation of the T cell immune response in individuals treated with the triple combination was observed.[1] It was concluded that, in the future, different subsets of individuals could be selected for treatment with either the nivolumab/chemotherapy combination or the situgalimab/chemotherapy combination based on the observed biomarker correlations. Treatment of unselected individuals with either of the dual combinations was not recommended.[1]

This study deserves praise because it made a major effort to detect biomarkers associated with benefit from either dual treatment arm that can lead the way for future therapy studies in groups of individuals with PDAC selected on the basis of these biomarkers. Importantly, the worse results of triple therapy can also be explained by the biomarker analyses indicating over-stimulation of the T cell immune response in individuals receiving triple therapy. As often is the case in immunotherapy, more is not always better. These clinical trial results are extremely important to make further progress in the treatment of this very hard to treat category of individuals with advanced PDAC.

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DECLARATION OF INTERESTS

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