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LETTER TO THE EDITOR

Family history of cancer and DNA damage response genes: Two sides of the same coin?

Dear Editor,

We read with interest the editorial by Zhu *et al.* about the possible positive predictive role of somatic alterations in DNA damage response and repair (DDR) genes for clinical benefit of immunotherapy with PD-1/PD-L1 immune checkpoint inhibitors in non-small cell lung cancer (NSCLC) patients.[1] The editors discussed the putative surrogate relationships between the immune sensitive phenotype (e.g. high tumor mutational burden) and somatic alterations of genes belonging to DNA repair systems, such as homologous recombination, mismatch excision repair (MMR), nucleotide excision repair, cell cycle checkpoints, Fanconi anemia DNA repair pathway, and others. Recently Teo *et al.* reported an impressive correlation between better clinical outcome and somatic DDR gene alterations in a cohort of advanced urothelial cancer patients treated with atezolizumab.[2] Interestingly, a higher response rate was found not only in patients whose tumors harbored known or likely deleterious DDR alterations but also in patients with DDR alterations of unknown significance when compared to patients whose tumors were wild type for DDR genes.[2] Despite the small sample size, DDR alterations (both deleterious and unknown) were associated with longer progression-free and overall survival.

Homologous recombination and MMR deficiencies are known as hallmarks of the best known syndromes of inherited cancer susceptibility, such as Lynch and breast–ovarian cancer syndromes (related to germline mutations of *MMR* genes and *BRCA1/2*, respectively).[3] Furthermore, much about cancer predisposition remains unknown; during their career every oncologist has surely come into contact with families with a suggestive incidence of malignancies, but without finding the alleged responsible germline mutation.

With this mind, we wondered if a family history of cancer and a diagnosis of metachronous and/or synchronous multiple neoplasms could be used as possible surrogate predictors of clinical benefit from anti-PD-1/PD-L1 treatments. In the preliminary analysis of the FAMI-L1 study, 211 advanced cancer patients (NSCLC, melanoma, and renal cell carcinoma) treated with anti-PD-1/PD-L1 agents were evaluated. We found that FHC was significantly related to better objective response rate, disease control rate, longer time to treatment failure, and overall survival.[4] Analogous findings were observed for a diagnosis of multiple neoplasms; however, the results did not reach statistical significance.[4] Clearly, our results are not conclusive; the aim of the preliminary analysis was only to test the hypothesis, describing from afar something that we are still not able to explain up close.

We are currently working on a larger dataset and have planned an analysis of the "burden of familiarity" in order to evaluate the hypothesis that the greater the number of positive lines, the better the immunotherapy outcome. In our opinion, the mechanisms that underlie our findings might be DDR genes alterations, even of unknown significance. In such a case, would germline testing with a dedicated gene panel be sufficient? If family history of cancer is a surrogate of DDR genes alterations, would it be easier to evaluate plasma samples rather than tumor specimens?

Disclosure

No authors report any conflict of interest.

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