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Response to Immunotherapy in Cancer Patient One Biomarker is not Enough

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ABSTRACT

Immunotherapy have led to astronomic changes in cancer treatment with several approval by the Food and Drug Administration for varied cancers. In the era of precision oncology, medical oncologist needs biomarkers to guide their prescription of these new treatments, and to select the right patient for these high-cost drugs. in this article we describe the available predictors biomarkers for Immune checkpoint therapies response and their limitations.

Immunotherapy have led to monumental changes in cancer treatment with several approval by the Food and Drug Administration (FDA) for varied cancers [1]. In the era of precision oncology, medical oncologist needs biomarkers to guide their prescription of these new treatments to select the right patient for these high-cost drugs.

Many studies reinforce programmed death-ligand 1 (PD-L1) expression, tumor-infiltrating lymphocytes (TILs), mismatch repair deficiency (MMRd) and tumor mutational burden (TMB) as predictive biomarkers to instruct the prescription of Immune Checkpoint Blockade (ICB) therapies [2]

But Many questions remain without any clear response; what is the more accurate biomarker for ICB use?

- Is TMB a more accurate, comprehensive biomarker since it is obtained throw NGS comparing to the others biomarkers obtained by IHC?
- Is there any relationship between the different biomarkers?
- Is ICB therapy advised for patients with MMRp / MSS, but with high TMB or PDL1 positive
- Should we do extensive analysis of MMRd / MSI-H, PD-L1, TMB and TILs for each tumor and prescribe ICB if one of them returned positive?
- Why some tumors didn't response to ICB despite they are expressing PDL1?

Therefore, it is mandatory continuing investigation for suitable biomarkers to predict the efficacy of immunotherapy and thus identify the patients who are most likely to respond to ICBs

Tumor-Infiltrating Lymphocytes (TILs)

TILs represent the important constituent of the tumor environment. Increased levels of TILs were associated with increased rates of response to neoadjuvant chemotherapy and improved prognosis for the molecular subtypes of TNBC and HER2-positive breast cancer, but not for patients with HR positive breast cancer. A threshold of 20% TILs was the most powerful outcome prognosticator of pathological completer response. In the literature patients with elevated infiltration density of TILs had an excellent prognosis after immunotherapy. Many studies suggest that immune-inflamed tumors (hot tumors) than immune-desert tumors (cold tumors), can inspire a robust immune response especially in Lung cancers [3,4]

Mismatch Repair Deficiency (MMRd)

MSI/ MMRd, is the consequence of the inactivation of mismatch repair genes, MSI detection can be done by immunohistochemistry (IHC) but NGS has also recently emerged. MSI-high status correlates with higher neoantigen expression which helps the immune system recognize tumors. MMRd have been identified in multitude of solid tumors, MMRd/MSI high have the particularity to predict the response for ICB regardless the type and site of tumor [5]. This biomarker is considered as a presage of response to ICB in stage IV colorectal cancer (CRC), stomach cancer and endometrial cancer (EC), in localized CRC it is a prognostic factor as well with a benefit in the OS 6. in stage IV EC MMRd combination of immunotherapy and chemotherapy is the standard of care on first line, the second line of treatment is dictated by the MMR status to use ICB as monotherapy or combined with TKI [6-9]. The FDA approved the use of pembrolizumab in all MSI tumors regardless the status of the others biomarkers, which is meaning that you can still prescribe ICBs even if the tumor is TMB low or PDL1 negative. PDL1+ expression was higher in MMRd CRC then in MMRp [10,11]. A study of 393 patients with advanced gastrointestinal cancers, genitourinary cancers or rare cancers showed that PD-L1+ expression was 38.9% in MMRd solid tumors compared with 15.2% in pMMR tumors [12]. In other studies, [13,14] the PD-L1+ rate varied from 12.1–35.2% in pMMR Gastric Cancer (GC) and from 46.7–60.0% in MMRd GC

Programmed Death-Ligand 1 (PD-L1)

PD-L1 is a biomarker correlated with immune system inhibition. PD-L1 positivity is a presage to response to immunotherapy. However, the heterogeneity of this biomarker emphasizes the need for further implements to predict the right patient for immunotherapy. The PDL1 status is considerably different among varied cancers, but also inside the same tumor (spatial heterogeneity)

Precise evaluation of PD-L1 status is important for proper treatment judgements. Misclassification of PD-L1 expression can be established by different factors such as expression heterogeneity [15].

PDL1 is not an accurate biomarker for many reasons:

1/several studies have described the efficacy of ICBs in PDL1- tumor of the cervix, lung and melanoma [16-18]

2/other study showed more percentages of PD-L1 positivity in the resected specimens compared to diagnostic biopsies [19].

3/Biopsies containing less than 100 cancer cells or older than three years may conduct to an underestimation of PD-L1 status [20].

4/ changeability between pathologist and over the different anatomical sites and variability during disease progression may play a role as well [21,22]

5/Also, this difference may be due to the antibodies used in the assessment of the PDL1 status. Antibody clone SP142 showed lower levels of PD-L1 expression compared with the 22C3 assay [23,24].

Tumor Mutational Burden (TMB)

TMB estimates the frequency of somatic mutation in cancer patient. high TMB correlates with elevated neoantigen status and recognition of cancer cells by T cells. It has been described in many cancers and has been correlated with improved response rate and prolonged survival for patients on ICBs [25]. TMB enlarges the proportion of patients who can be candidates for immunotherapy. TMB has been extensively considered in melanoma, lung and bladder cancers [26-29].

But what are the benchmarks to distinguish between low and high TMB? Some authors are using the threshold of 10 somatic mutations per mega base, some others 16 others 6 [30-32]. Relationship between TMB and PD-L1 expression may vary among different cancers, there are discrepant data regarding the relationship between PD-L1 expression and TMB. A study in the Bloomberg-Kimmel Institute for Cancer Immunotherapy [33] showed that PD-L1 expression and TMB are not absolutely correlated within most cancer subtypes, and they show only a marginal relationship. Across distinct cancers, PD-L1 expression and TMB have distinct effects on the response rate to ICBs. further study are necessary to analyze the correlation between TMB and PD-L1 expression in different cancers.

Yoonet all [34] showed that in various cancers, a correlation between TMB and PD-L1 status. This Relationship may differ among different cancer site, with a high compatibility found in Gastric Cancers and EC and a frail association with pancreatic cancer and kidney cancer [35-37].

Conclusion

Ther is an unmet need to presage patients' responses to ICBs using biomarkers to select the right patients for this treatment, there is a discrepant result between the available biomarkers used in the clinic. Researchers need to investigate for predictive clinically trustworthy biomarkers, practically in the daily practice, by merging all the available markers you can be more confident not excluding your patients from responding to immunotherapy drugs.

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