Pan Arab Journal of Oncology

Editorial

Tumor mutational burden: a new predictive biomarker for immunotherapy

Abdel Hadi El Hajjar

Université Saint-Joseph, Faculté de Médecine, Damascus Street, Beirut, Lebanon

Corresponding Author

Abdel Hadi El Hajjar
Corniche El Mazraa,
Beirut, Lebanon.
+ 961 03 289294
abedelhajjar@hotmail.com

In recent years, immunotherapies have shown great promise in cancer treatment. These agents increase the antitumor activity of the immune system throughout many mechanisms. Well-known agents, checkpoint inhibitors, are approved molecules in a wide spectrum of cancer types such as melanoma, non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer and colorectal cancer (CRC). Whether by inhibiting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1), they promote T cell activation against tumor cells. (1) But, this treatment is expensive and generate immune-related adverse events, especially with combination regimens. Thus, the challenge is to select patients eligible for immunotherapy.

Development of biomarkers to select patients that might benefit from immunotherapy regimen is already under way. The three leading biomarkers are PD-L1 expression, mismatch repair deficiency (MMR-d) or microsatellite instability status (MSI) and tumor mutational burden (TMB). Other biomarkers include CD 8 infiltrate density, T-cell receptor clonality, RNA level changes, and protein level changes. (2),(3),(4). A comparison of TMB and MSI showed that the majority of MSI-high tumors (85%) had TMB high but the converse was not true (5). Consequently, tumor mutational burden might be a very accurate biomarker that predicts response to immunotherapy.

The tumor mutational burden (TMB) is defined as "the number of somatic mutations per Mb of the genome and is used to represent accumulation of somatic mutations over the life of the tumor"(6). The rationale behind the use of TMB as a biomarker is that tumors with high TMB tend to express more neoantigens. Those antigens can be recognized by the immune system once checkpoint inhibitors are administered. An extensive literature search gathering data from 27 tumor types showed a significant correlation between TMB and objective response rate ($p< 0.001$) with anti-PD-1 therapies (7). Goodman et al. proved that cancers with higher TMB have better response rate (RR), progression free survival (PFS) and overall survival (OS) with immunotherapy especially with PD-1/PD-L1 blockade. But the outcome after combination of multiple immunotherapies is independent of TMB (8).

The most precise method to determine TMB is by whole exome sequencing (WES). However, this method is expensive. Recent studies therefore tested the efficiency of next generation sequencing (NGS) panel in determining TMB. An

analysis of 100 000 human cancer genomes showed that a comprehensive genome profiling (CGP) targeting 1.1 Mb can estimate accurately TMB (9). Other studies also proved that sequencing a panel of a certain number of genes can estimate the TMB (10),(11). Foundation One Cdx (F1CDx) is a next generation sequencing diagnostic device that got FDA approval. It detects mutations in 324 genes, microsatellite status and TMB using DNA obtained from tumor tissue. Then, it can identify patients who can benefit from a certain targeted therapy.

TMB was mostly investigated in non-small cell lung cancer (NSCLC). Currently, PD-L1 expression is the most used biomarker to predict response to immune checkpoint inhibitors. However, a large amount of PD-L1 negative tumors respond to checkpoint inhibitors (12). A biomarker with more predictive value should therefore be established. Studies revealed that patients with high TMB showed better response to Nivolumab plus Ipilimumab than Nivolumab monotherapy (13). In a phase 3 trial, the one year progression free survival rate was 42.6 % with Nivolumab plus Ipilimumab versus 13.2 % with chemotherapy (14). This emphasizes the efficiency of TMB as a predictive biomarker in NSCLC.

Recent studies are now testing the use of TMB as a predictive biomarker in other tumor types such as colorectal cancer (CRC). MSI high proved to be an efficient biomarker and predicted favorable response to checkpoint inhibitors (1). But, a recent study showed that MSI tumors are all TMB and 3% of microsatellite stable (MSS) tumors are also TMB high. Therefore, TMB can expand the population of CRC patients profiting from immunotherapy (15). In fact, TMB high status may also be attributed to a hypermutating phenotype such as POLE mutation. Note also that in CRC, TMB low status might be a predictive biomarker with chemotherapy (16).

Reports of clinical cases illustrated the predictive role of TMB in other type of cancers. Examples include the response of high TMB neuroendocrine cervical carcinoma to Nivolumab and Stereotactic Body Radiation Therapy (17), high TMB platinum-resistant ovarian cancer to anti PD-L1 (18) and high TMB adrenocorticotropic hormone-secreting pituitary carcinoma to Ipilimumab and Nivolumab (19). Further studies need to confirm the role of TMB as a predictive biomarker in those cancer types.

With the outburst of innovation in the oncology field, recent studies are also testing TMB assessment in peripheral blood rather than cancer tissue. Gandara et al. proved that high TMB assessed from peripheral blood is a predictive biomarker for Atezolizumab in NSCLC (20), (21).

Some ongoing trials are aiming to further establish TMB as a solid predictive biomarker for immunotherapy. For example, NCT03638297 is a phase 2 study testing the efficacy of PD-1 antibody and cox inhibitor in MSI high or TMB high CRC. Its primary outcome is 6 month response rate. Another clinical trial (NCT03516981) is investigating the efficiency of Pembrolizumab and Lenvatinib in advanced NSCLC according to gene expression profile (GEP) and TMB profile. It is also a phase 2 study recruiting 192 participants and its primary outcome is to determine objective response rate (ORR).

Last, let us not forget that, like every diagnostic tool, TMB use as a biomarker has its unique limitations. First, tissue specimen might not always be available. Second, there are multiple testing platforms. Also, determining TMB status is a relatively expensive procedure. Other disadvantages include genomic heterogeneity of tumors and longer turnaround time (22).

References

1. Hajjar AHE, Barouky E. Checkpoint inhibitors: a new therapeutic arm in mismatch repair deficient metastatic colorectal cancers. 2017;10(3):3.
2. Yi M, Jiao D, Xu H, Liu Q, Zhao W, Han X, et al. Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. Mol Cancer [Internet]. 2018 Dec [cited 2018 Aug 26];17(1). Available from: https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-018-0864-3
3. Khagi Y, Kurzrock R, Patel SP. Next generation predictive biomarkers for immune checkpoint inhibition. Cancer Metastasis Rev. 2017 Mar;36(1):179–90.
4. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016 Dec;17(12):e542–51.
5. Frampton GM, Fabrizio DA, Chalmers ZR, Sun JX, Miller VA, Stephens PJ. Assessment and comparison of tumor mutational burden and microsatellite instability status in >40,000 cancer genomes. Ann Oncol [Internet]. 2016 Oct [cited 2018 Aug 26];27(suppl_6). Available from: http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdw363.01/2798777/Assessment-and-comparison-of-tumor-mutational
6. Mola N, Jones W, Weigman V. Tumor Mutational Burden: Guidelines for derivation and robustness of measurement. :1.
7. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med. 2017 Dec 21;377(25):2500–1.
8. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598–608.
9. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med [Internet]. 2017 Dec [cited 2018 Aug 26];9(1). Available from: http://genomemedicine.biomedcentral.com/articles/10.1186/s13073-017-0424-2
10. Hatakeyama K, Nagashima T, Urakami K, Ohshima K, Serizawa M, Ohnami S, et al. Tumor mutational burden analysis of 2,000 Japanese cancer genomes using whole exome and targeted gene panel sequencing . Biomed Res. 2018 Jun 1;39(3):159–67.
11. Zhuang W, Ma J, Chen X, Wang G, Lu J, Chen Y, et al. The Tumor Mutational Burden of Chinese Advanced Can-

cer Patients Estimated by a 381-cancer-gene Panel. J Cancer. 2018;9(13):2302–7.
12. Cyriac G, Gandhi L. Emerging biomarkers for immune checkpoint inhibition in lung cancer. Semin Cancer Biol [Internet]. 2018 May [cited 2018 Aug 26]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1044579X1730250X
13. Hellmann MD, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell. 2018 May;33(5):853-861.e4.
14. Hellmann MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018 May 31;378(22):2093–104.
15. Fabrizio DA, George Jr TJ, Dunne RF, Frampton G, Sun J, Gowen K, et al. Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. J Gastrointest Oncol. 2018 Aug;9(4):610–7.
16. Pai SG, Carneiro BA, Chae YK, Costa RL, Kalyan A, Shah HA, et al. Correlation of tumor mutational burden and treatment outcomes in patients with colorectal cancer. J Gastrointest Oncol. 2017 Oct;8(5):858–66.
17. Sharabi A, Kim SS, Kato S, Sanders PD, Patel SP, Sanghvi P, et al. Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. The Oncologist. 2017 Jun;22(6):631–7.
18. Morse CB, Elvin JA, Gay LM, Liao JB. Elevated tumor mutational burden and prolonged clinical response to anti-PD-L1 antibody in platinum-resistant recurrent ovarian cancer. Gynecol Oncol Rep. 2017 Aug;21:78–80.
19. Lin AL, Jonsson P, Tabar V, Yang TJ, Cuaron J, Beal K, et al. Marked response of a hypermutated adrenocorticotropic hormone-secreting pituitary carcinoma to ipilimumab and nivolumab. J Clin Endocrinol Metab [Internet]. 2018 Aug 1 [cited 2018 Aug 26]; Available from: https://academic.oup.com/jcem/advance-article/doi/10.1210/jc.2018-01347/5062271
20. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med [Internet]. 2018 Aug 6 [cited 2018 Aug 26]; Available from: http://www.nature.com/articles/s41591-018-0134-3
21. Das M. Blood-based tumour mutational burden analysis in NSCLC. Lancet Oncol [Internet]. 2018 Aug [cited 2018 Aug 26]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204518306156
22. Steuer CE, Ramalingam SS. Tumor Mutation Burden: Leading Immunotherapy to the Era of Precision Medicine? J Clin Oncol. 2018 Mar;36(7):631–2.