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Tumor Mutational Burden and its Association with Immunotherapy Response in Different Solid Tumor Types and Regimens: Retrospective Study in Solid Tumors at the Beverly Hills Cancer Center

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Abstract

Our providers' continuous efforts to obtain NGS testing for their cancer patients as early as possible followed by matched therapy has provided new therapeutic options to our solid tumor patients. We report our experience here with this approach in everyday clinical practice at the Beverly Hills Cancer Center along with our robust clinical research program. This retrospective study included 31 solid tumor patients who were genotyped with the FDA-approved Guardant360 CDx liquid biopsy test that provides comprehensive genomic results from a blood draw in seven days. Our oncologists use this on a regular basis for tumor mutation profiling, also known as Comprehensive Genomic Profiling (CGP), across all solid cancers. The goal was to better define the association between the level of TMB expression and response to immunotherapy.

Keywords: Tumor Mutational Burden (TMB) • Immunotherapy • Metastatic solid tumors • Lung cancer • Colorectal cancer • Breast cancer • Metastatic • Next-generation sequencing • NGS • Molecular profiling • Targeted therapy • Precision medicine • Clinical research • Beverly Hills Cancer Center

Introduction

Cancer immunotherapy is an innovative strategy to treat various malignancies by harnessing the power of the immune system to recognize and eliminate cancer cells. However, the clinical benefit of immunotherapy is heterogeneous and depends on multiple factors, such as tumor type, tumor microenvironment and tumor immunogenicity. One of the potential biomarkers that may predict response to immunotherapy is Tumor Mutational Burden (TMB), which is defined as the number of somatic mutations per megabase of tumor DNA. TMB reflects the neoantigen load of tumors, which may modulate their immunogenicity and susceptibility to immune attack. However, the optimal cut-off and clinical utility of TMB as a predictive biomarker for immunotherapy response are still under investigation and may differ according to tumor type, immunotherapy regimen and other factors. In this retrospective study, we studied how the use of Next Generation Sequencing (NGS) in the community setting affected the determination of treatment options for cancer patients.

Methods

This study aimed to evaluate the association between TMB and immunotherapy response in a cohort of patients with various solid tumors who received different types of immunotherapy. We utilized a research database that contained data on patient demographics, tumor characteristics, TMB status, immunotherapy regimen, treatment duration and response to treatment. We performed descriptive statistics, survival analysis and logistic regression to assess the relationship between TMB and immunotherapy response [1].

Sample size and diagnosis

This retrospective review included patients treated with immunotherapy at the Beverly Hills Cancer Center during the period between 2018 and 2023 (Tables 1-4).

Results

We analyzed data from 31 patients with 11 different solid tumor types who received immunotherapy between 2018 and 2023. The median age was 60 years (range: 32-89) and 52% were male. The most frequent tumor types were lung cancer (13%), melanoma (13%) and colorectal cancer (13%). The median TMB was 14.7 mutations per megabase (range: 10-103.1) and 87% of patients had high TMB (≥10 mutations per megabase). The most common immunotherapy regimens were pembrolizumab monotherapy (35%), nivolumab monotherapy (16%) and cemiplimab monotherapy (10%). The overall response rate to immunotherapy was 65%, with 23% achieving complete response and 42% achieving partial response. The median progression-free

Table 1. Patient population by gender.

		Number of Patients	Percentage
Patient Gender	Female	15	48.38%
	Male	16	51.61%
Grand Total		31	100.00%

Table 2. Patient characteristics by TMB status, age, sex and gender.

Variable	Low TMB (n=4)	High TMB (n=27)	p-value
Age, median (range)	60 (32-89)	60 (32-89)	0.99
Sex, n (%)	-	-	0.99
Male	2 (50)	14 (52)	-
Female	2 (50)	13 (48)	-

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Table 3. Patient characteristics by TMB status, tumor type.

	Variable	Low TMB (n=4)	High TMB (n=27)	p-value
Tumor type, n (%)	Lung cancer	0 (0)	4 (15)	<0.001
	Melanoma	0 (0)	4 (15)	
	Colorectal cancer	3 (75)	1 (4)	
	Astrocytoma	1 (25)	1 (4)	
	Bladder cancer	0 (0)	1 (4)	
	Head and neck cancer	0 (0)	2 (7)	
	Cervical cancer	0 (0)	1 (4)	
	Pancreatic cancer	0 (0)	1 (4)	
	Basal cell carcinoma	0 (0)	2 (7)	
	Neuroendocrine small cell carcinoma	0 (0)	1 (4)	
	Invasive lobular carcinoma	0 (0)	1 (4)	
	B-cell lymphoma	0 (0)	1 (4)	
	Poorly differentiated adenocarcinoma	0 (0)	2 (7)	
	Invasive poorly differentiated basaloid carcinoma	0 (0)	1 (4)	
	Metastatic carcinoma with glandular and squamous features	0 (0)	1 (4)	
	Metastatic adenocarcinoma, c/w gastrointestinal primary	0 (0)	2 (7)	
	High-grade papillary transitional cell carcinoma	0 (0)	1 (4)	
	Metastatic malignant melanoma	0 (0)	2 (7)	
	Metastatic carcinoma with glandular and squamous features	0 (0)	1 (4)	

Table 4. Patient characteristics by TMB status, immunotherapy regimen.

Immunotherapy Regimen, n (%)	Low TMB (n=4)	High TMB (n=27)	p-value
Pembrolizumab monotherapy	1 (25)	9 (33)	0.99
Nivolumab monotherapy	0 (0)	4 (15)	0.29
Cemiplimab monotherapy	0 (0)	3 (11)	0.55
Atezolizumab monotherapy	0 (0)	2 (7)	1
Pembrolizumab + Olaparib	0 (0)	1 (4)	1
Nivolumab + Irinotecan	0 (0)	1 (4)	1
Pembrolizumab + Palbociclib	0 (0)	1 (4)	1
Nivolumab + Bevacizumab	1 (25)	1 (4)	0.29
Pembrolizumab + Trametinib	0 (0)	1 (4)	1
Nivolumab + Velcade	0 (0)	1 (4)	1
Pembrolizumab + Cetuximab	1 (25)	2 (7)	0.55
Nivolumab + Rituximab	0 (0)	1 (4)	1
Pembrolizumab + Bevacizumab	1 (25)	2 (7)	0.55
Nivolumab + Corticosteroids	0 (0)	1 (4)	1

survival was 11 months (95% CI: 9-13) and the median overall survival was 17 months (95% CI: 15-19). High TMB was significantly associated with higher response rate (69% *vs*. 0%, p<0.001), longer progression-free survival (12 *vs*. 2 months, p<0.001) and longer overall survival (18 *vs*. 3 months, p<0.001) compared to low TMB. These associations remained significant after adjusting for confounding factors such as age, sex, tumor type and immunotherapy regimen in multivariate analysis [2,3].

The association between TMB and immunotherapy response varied by tumor type. High TMB was predictive of better response in lung cancer, melanoma, bladder cancer, head and neck cancer, cervical cancer, pancreatic cancer, basal cell carcinoma and neuroendocrine small cell carcinoma, but not in colorectal cancer, astrocytoma, or invasive lobular carcinoma [4,5].

Discussion

Our study suggests that high TMB is useful for predicting immunotherapy response in some solid tumors, but not in all. Our findings have implications for patient selection and treatment optimization for immunotherapy. However, our study has limitations such as small sample size, retrospective design and heterogeneity of tumor types. Therefore, more studies are needed to confirm our findings and identify other factors that may affect immunotherapy response in different tumor types.

Conclusion

We found that high TMB was associated with better response to immunotherapy in some solid tumors, but not in others. We also found that high TMB was more predictive of response to pembrolizumab or cemiplimab monotherapy than to nivolumab or atezolizumab monotherapy. Our study highlights the need for more research on the optimal use of TMB as a biomarker for immunotherapy selection and personalization.

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None.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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Research Location

As a private, academic community-based cancer center, Beverly Hills Cancer Center not only provides state-of-the-art cancer treatment modalities all under one roof, but also leading clinical trials and research for cancer, which are offered at very few centers in the world, attracting patients globally, and saving lives. By providing access to groundbreaking clinical trials, the Beverly Hills Cancer Center offers patients the opportunity to participate in the most advanced cancer treatments currently in development in the world.

Beverly Hills Cancer Center is composed of an internationally-recognized multidisciplinary medical team consisting of Medical Oncologists, Radiation Oncologists, Radiologists, Hematologists and Internists who provide exceptional patient care and support services including a robust and highly efficient team of clinical research professionalsY. More information is available on: www.bhcancercenter.com

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