Case Report

A Patient with a microsatellite stable (MSS) and high mutational burden metastatic colorectal cancer responding to checkpoint inhibitor therapy

Introduction

The checkpoint inhibitors are thought to act through activation of a cytotoxic immune response that has been inhibited through tumor expression of PD-L1 and PD-L2. Various molecular markers appear to predict the likelihood of response to checkpoint inhibitors. For example, for non-small-cell lung cancer (NSCLC), PD-L1 or PD-L2 expression are predictors of checkpoint inhibitor efficacy.[1] In contrast tumor mutational burden is a predictor of response to checkpoint inhibitor therapy in patients with glioblastoma multiforme.[2]

Metastatic colorectal cancer (mCRC) remains the second most common cause of cancer death in the US and there are limited therapeutic options. The checkpoint inhibitor, Pembrolizumab was recently given FDA "breakthrough therapy designation" but only for the treatment of patients with mCRC whose tumors demonstrate deficient mismatch repair (dMMR) or microsatellite instability (MSI). The FDA endorsement was based on a phase II study showing that in patients with dMMR an objective response rate of 40% was seen, while in those patients with proficient mismatch repair (pMMR) or microsatellite stability (MSS)mCRCs the response rate was 0%.[3]

Here we report a first case of a patient with an MSS but an extremely high mutational burden mCRC whose tumor demonstrated a dramatic biochemical response and prolonged radiographic stability resulting from checkpoint inhibitor therapy. If additional patients are reported with these same molecular abnormalities then clinical trials might also include such patients for checkpoint inhibitor therapy with the hope that like dMMR, high mutational burden predicts responsiveness to checkpoint inhibitors for patients with mCRC.

Clinical case

JR is a 66-year-old patient who underwent a right hemicolectomy and omental biopsy in October 2014 and was found to have a cecal moderately differentiated adenocarcinoma (pT4aN1cM1). A CT scan showed diffuse peritoneal implants and palliative chemotherapy was initiated with cetuximab and FOLFIRI (5-FU/leucovorin/irinotecan) beginning in May 2015. In January of 2016 the patient showed a rising CEA level from 53.3NG/ML in August 2015 to 226.7NG/ML in February 2016 (normal, 3.0 NG/ML). A CT scan demonstrated enlarging multiple peritoneal nodules.

The patient underwent next generation sequencing and was found to have 42 somatic genomic alterations identified. However MSS was confirmed in his tumor (Foundation One, Inc, Cambridge, MA 02141). The patient's tumor showed a remarkably high tumor mutation burden (TMB) of 398 mutations per megabase(Low mutational burden is 0 to 5 mutations per megabase; intermediate burden is 6 to 19 mutations per megabase; high is greater than or equal to 20 mutations per megabase).

Checkpoint inhibitor therapy with nivolumab was initiated and a follow-up CT scan in June 2016 showed stability of the peritoneal

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metastases. Also, the patient's CEA had improved to 36.8 NG/ML (from 226 NG/ML) and he continued taking the nivolumab. A repeat CT scan in October 2016 again showed stable peritoneal metastasis. His CEA improved further to 5.7.

Conclusions

Checkpoint inhibitor therapy is approved for use in mCRCs that demonstrates MSI or dMMR. Our patient had MSS. However our patient's tumor did demonstrate an extremely high mutation burden, and mutation burden is a predictor of response to checkpoint inhibitor therapy for other malignancies.[2] The responsiveness is presumably because, like tumors with dMMR or those with high PD-L1 expression, an enhanced cytotoxic response is generated toward the tumor that is mitigated by the tumor until initiation of the checkpoint inhibitor.

The checkpoint inhibitors are endorsed by the FDA and the National Comprehensive Cancer Network where markers predictive of response are demonstrated, such as PD-L1 over expression,[1] but only endorsed for treating mCRC if dMMR (or MSI) is demonstrated.[3] If others report similar cases of pMMR with high mutational burden mCRCs responding to checkpoint inhibitor therapy, future trials should include patients with this molecular profile as a way of determining whether, like patients with dMMR, such patients have a high likelihood of benefit from checkpoint inhibitor therapies.

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Conflict of interest

The author declares no conflict of interest.

References

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