Mismatch Repair Deficiency Testing for Immune Checkpoint Blockade Therapy: Immunohistochemistry vs Microsatellite Instability

#3022

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Background

DNA mismatch repair deficiency (dMMR) can be tested by immunohistochemistry (IHC) or microsatellite instability (MSI). While either IHC or MSI is adequate for establishing Lynch syndrome, the relevance of discordant results in selecting patients for immune checkpoint treatment is unknown. We investigated MSI and IHC in detecting dMMR and correlated with PD-L1 expression.

Methods

Community-based practice tissue samples were submitted for PD-L1 expression and dMMR by both IHC and MSI. PD-L1 testing was performed by IHC using clone 22C3, dMMR using IHC against four MMR proteins (MLH1, MSH2, MSH6, and PMS2), and MSI using PCR with five Bethesda markers.

Key Points

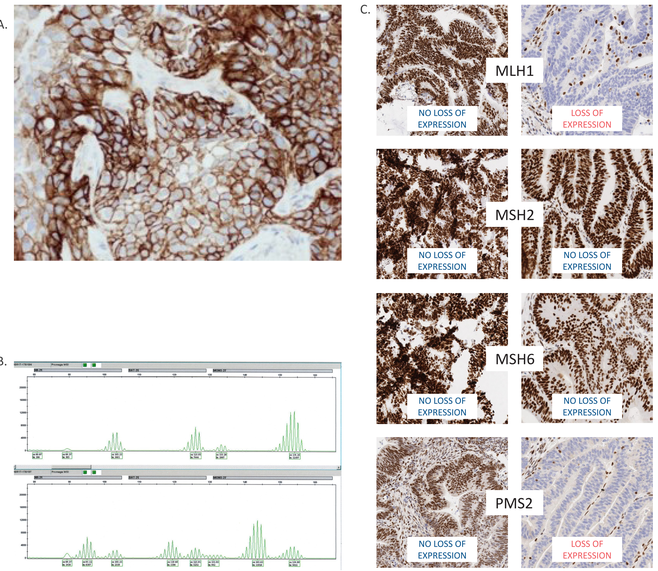
- There is significant correlation between PD-L1 expression and dMMR as detected by MSI, but not by IHC testing.
- Discrepancy between MSI and IHC testing for dMMR is significant statistically (P<0.0001).
- There is an established association between tumor mutation burden and MSI.
- dMMR testing may miss 8.9% (false negative; FN) of the MSI-positive cases and may give false positive (FP) results in 2.6% of negative cases.
- MSI should be considered the gold standard for dMMR testing for checkpoint blockade therapy consideration.
- Clinical trials are needed to determine which method is more accurate for predicting response to checkpoint inhibitors.

Results

- Of the 396 cases tested for both PD-L1 and dMMR by IHC, 18 (4.5%) were reported dMMR positive.
- Of the 610 cases tested for both PD-L1 and dMMR by MSI, 27 (4.4%) were dMMR positive (at least one MMR protein expressed at ≤ 6%).
- There was no statistically significant correlation between PD-L1 expression and the presence or absence of dMMR as detected by IHC.
- Patients with MSI had significantly higher PD-L1 positive cells when PD-L1 expression is considered as a continuous variable (P=0.04), and at cut-offs of 5% (P=0.003) and 10% (P=0.004).
- When a cut-off point of 6% for IHC is used, 8.9% of positive cases by MSI were negative (FN) by IHC and 2.6% of MSI negative cases were positive (FP) by IHC.
- This difference between cut-off points was statistically significant (P=0.0008 for 20% and P=0.0001 for 30% cut-off).

Positive and Negative Correlations of 21 Genes

A. PD-L1 expression by IHC; B. MSI; C. dMMR by IHC



Positive and Negative Correlations of 21 Genes

- Comparison of false positive and negative results depending on dMMR IHC cut-off used.
- Each of the 3 result rows represent the results of cut-offs of 6%, 20%, and 30% cell staining by IHC.
- Subsequent columns enumerate the number of positive and negative of each of these by MSI by PCR. From these totals, using MSI results as the gold standard, the number of false negatives and positives from the IHC data were calculated.

dMMR by IHC cut-off		MSI			% Positive		% IHC FN	% IHC FP
		Pos	Neg	Total	by MSI	by IHC		
6%	Pos	267	16	283	32.38	31.27	8.9	2.6
	Neg	26	596	622				
20%	Pos	280	22	302	32.38	33.37	4.4	3.6
	Neg	13	590	603				
30%	Pos	284	35	319	32.38	35.25	3.1	5.7
	Neg	9	577	586				
Total		293	612	905				

[1] FP ≡ false positive; [2] FN ≡ false negative

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