Pembrolizumab for non-Small-cell lung cancer

Pembrolizumab, demonstrated durable response and prolonged OS especially in non-Small cell lung cancer treatment with high expression of PD-1, thereby suggests a new treatment paradigm. However, many issues remain to be explored, including the identification of other robust biomarkers that can accurately predict the immune-responsiveness of tumors. Along with the identification of predictive biomarkers, further understanding of the tumor microenvironment is necessary to improve treatment outcomes through combinations of immunotherapy or combined with other targeted therapies [1)].

Patients with NSCLC of PS2 are a group of patients of unmet therapeutic need. The PePS2 trial shows that pembrolizumab can be safely administered to these patients, with no increase in the risk of immune-related or other toxicities. Efficacy outcomes are at least as good as those in patients with PS0-1 and the data provides clinicians with the confidence to incorporate pembrolizumab into the treatment pathway of patients with NSCLC of PS2 [2)].

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study included 60 patients with NSCLC who underwent first or second line immunotherapy with pembrolizumab or nivolumab. Formalin-Fixed Paraffin-Embedded materials were collected before the start of immunotherapy. We examined relative expression of microRNAs (miR-141, miR-200a, miR-200b, miR-200c, miR-429, miR-508-3p, miR-1184, miR-1255a) and PD-L1 mRNA expression. Copy number variation (CNV) of PD-L1 gene by qPCR and FISH methods were assessed. Two single nucleotide polymorphisms (SNPs) in promoter region of PD-L1 gene (rs822335 and rs822336) were examined. Expression of PD-L1 protein on tumor cells was assessed by immunohistochemistry (IHC). The response rate to immunotherapy and progression free survival (PFS) measured in weeks and overall survival (OS) measured in months from the start of immunotherapy were evaluated.

Results: Response to immunotherapy was observed in nine patients (15%, including one complete response), disease stabilization in 22 patients (36.7%), and progression in 29 patients (48.3%). Significantly higher (p=0.015) expression of miR-200b and significantly lower (p=0.043) expression of miR-429 were observed in responders compared to patients who did not respond to immunotherapy. The median PFS in the whole group of patients was 16 weeks, and the median OS was 10.5 month. In univariate analysis, the median PFS was significantly higher in patients with high miR-200b expression (HR=0.4253, 95%CI: 0.1737-1.0417, p=0.05) and high miR-508 expression (HR=0.4401, 95%CI: 0.1903-1.0178, p=0.05) and with low expression of miR-429 (HR=0.1288, 95%CI: 0.01727-0.9606, p=0.0456) compared to patients with low and high expression of these molecules, respectively. The median OS was higher in patients with low expression of miR-429 (HR=0,6288, 95%CI: 0,3053-1,2949, p=0.06) compared with patients with high expression of this microRNA. In multivariate analysis, we found that patients with PD-L1 expression on ≥1% of tumor cells compared to patients without PD-L1 expression on cancer cells had a significantly lower risk of progression (HR=0.3857, 95%CI: 0.1612-0.9226, p=0.0323) and death (HR=0.377, 95%CI: 0.1636-0.8688, p=0.022).

Conclusion: The miR-200b and miR-429 molecules in tumor cells seem to have greatest impact on the

effectiveness of immunotherapy in NSCLC patients [3].

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analyzed tumor and edema volume in 18 non-Small-cell lung cancer. (NSCLC) and 18 melanoma patients with untreated brain metastases treated with pembrolizumab on a phase II clinical trial. Melanoma brain metastases were stained with anti-CD34 to assess vessel density and its association with edema. We employed an in vitro model of the blood-brain barrier using short-term cultures from melanoma brain and extracranial metastases to determine tight junction resistance as a measure of vessel leakiness.

Results: Edema volumes are similar in NSCLC and melanoma brain metastases. While larger tumors tended to have more edema, the correlation was weak (R2 = 0.30). Patients responding to pembrolizumab had concurrent shrinkage of edema volume and vice versa (R2 = 0.81). Vessel density was independent of the degree of edema (R2 = 0.037). Melanoma brain metastases cells in culture caused loss of tight junction resistance in an in vitro blood-brain barrier model system in some cases, whereas extracerebral cell cultures did not.

Conclusions: Edema itself should not preclude using anti-PD-1 with caution, as sensitive tumors have resultant decreases in edema, and anti-PD-1 itself does not exacerbate edema in sensitive tumors. Additional factors aside from tumor mass effect and vessel density cause perilesional edema. Melanoma cells themselves can cause decline in tight junction resistance in a system void of immune cells, suggesting they secrete factors that cause leakiness, which might be harnessed for pharmacologic targeting in patients with significant perilesional edema [4].

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