Immunotherapy and Biomarker for Efficacy in Lymphoma

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Abstract

Immune Checkpoint Inhibitor (ICI), especially programmed cell-death protein 1 ligand 1 (PD-L1)/PD-L2 and the programmed cell-death protein 1 (PD-1) axis inhibitor, has become an essential part of treatment for patients with solid tumors, including melanoma, lung cancer and gastric cancer. As for hematological malignancies, ICI has also been introduced as one of salvage therapy against relapse or refractory (r/r) classical Hodgkin lymphoma (CHL). However, trials addressing the clinical efficacy of ICI against other types of lymphoma are still limited, and it has not been fully elucidated whether biomarkers currently used in solid tumors are also clinically applicable for lymphomas to predict the efficacy of these novel therapies. In this review, we introduce some types of lymphomas which potentially have sensitivity to ICI and discuss potential biomarkers to predict these therapies.

Keywords: Hematologic malignancies; Immunotherapy; Programmed cell-death protein 1(PD-1)

Extranodal NK/T Cell Lymphoma, Nasal Type

Overview

Extranodal NK/T cell lymphoma, nasal type (ENKTL) is an aggressive lymphoma derived from NK cells whi fscallclbapeidate wll peÒ

of patients [13]. Gene expression profiling for EBV-positive DLBCL shows constitutive activation of the NF-kB pathway [14]. LMP-1, one of the EBV oncoprotein, plays an important role also in this activation, while CD79B and MYD88 mutations are rarely observed in EBV-positive DLBCL, which are 2 upstream components of the NF-kB pathway and are often found in the activated B-cell type of DLBCL [8,14,15]. High prevalence of TET2 and DNMT3A mutations are also reported, indicating the possible involvement of deregulated DNA methylation and demethylation process in this disease [8]. Moreover, Kataoka et al. also reported that PD-L1/PD-L2 genetic alterations are significantly frequent in EBV-positive DLBCL patients (5 out of 27) compared to EBV-negative DLBCL patients (1 out of 48) ($P<0.05$) [8]. PD-L1/PD-L2 SVs are also associated with upregulation of the NF-kB signaling pathway [16]. As with DLBCL-NOS, anthracycline-based chemotherapy including cyclophosphamide, doxorubicin, vincristine and prednisone with rituximab (R-CHOP) regimen is also used against EBV-positive DLBCL as standard 1st line treatment, however, the prognosis of EBV-positive DLBCL patients remains poor (median survival: 6-12 months) [1].

ICI for patients with EBV-positive DLBCL and potential biomarkers to predict ICI efficacy for patients with EBV-positive DLBCL

Clinical efficacy of single agent ICI against DLBCL, NOS is generally disappointing [17]; a phase 2 study of nivolumab which included r/r DLBCL patients relapsed after autologous stem cell transplantation (ASCT) showed the overall response rate of 10% without any complete responses [18]. These results are in line with another study, in which clinical efficacy of pembrolizumab was evaluated for r/r DLBCL patients [NCT003340766].

Considering the biological characteristics, EBV-positive DLBCL may be the subset of DLBCL which m ɋþBCy od Ibe

antibodies PD-1 inhibitors may further improve the efficacy of PD-1 blockade, considering that expression of LAG3 is thought to be related to a resistance to PD-1 blockade [35,36]. Clinical trials to examine the clinical efficacy of PD-1 and LAG-3 blockade combination therapy are currently ongoing [NCT02061761, NCT03598608].

Primary Mediastinal B-Cell Lymphoma

Overview

Primary mediastinal B-cell lymphoma (PMBL) is a non-Hodgkin lymphoma derived from thymic medullary B cells [1]. PMBL often shares its clinical, transcriptional, molecular biological features with CHL, while PMBL is not relevant with EBV infections [37]. As with CHL, the constitutive activation of the NF-kB pathway and JAK-STAT pathway are observed, and copy number alterations of the chromosome 9p24.1 are also frequently observed, while rearrangement of chromosome 9p24.1 is more commonly observed in PMBL patients than in CHL patients [38-46]. CIITA is known to be a representative partner gene of rearrangement [46]. In addition, unlike CHL, NFKB1A mutations are absent in PMBL, which indicate that there may be different mechanisms of the constitutive NK-kappa B activation pathway than CHL [47]. Anthracycline-based chemotherapy (R-CHOP and R-EPOCH (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone with rituximab)) has improved the long term outcome of PMBL patients, however, the efficacy of salvage therapy for r/r PMBL is limited; the ORR of conventional salvage chemotherapy and autologous stem cell transplantation (ASCT) for r/r PMBL is only 25% and 2-year post-ASCT OS is 15% [48].

ICI for patients with PMBL and potential biomarkers to predict ICI efficacy for patients with PMBL

Two prospective study revealed the efficacy of ICI for PMBL, in which the ORR of pembrolizumab for r/r PMBL were reported to be 45%-48% with CR rate of 13%-33% [49,50].

CHL and PMBL have higher tumor mutational burden (TMB) and microsatellite instability (MSI) compare[illegible] has'n to[illegible]

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Conclusion

We have reviewed several subtypes of lymphomas in terms of potential target of ICI. Further studies are warranted to reveal the clinical efficacy of ICI for lymphomas except for CHL and to detect potential biomarkers. Combining ICI with small molecules or chimeric antigen receptor T cell therapy may further potentiate its clinical role in treatment for lymphomas.

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