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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 or cytotoxic T cells, and is strongly associated with Epstein-Barr virus (EBV) infection [1]. In ENKTL, EBV is present in a clonal episomal form with type II latency (EBNA1+, EBNA2-, LMP1+), which results in activation of NF-kB pathway via LMP1 overexpression, finally leading to PD-L1 expression in tumor cells [1]. In previous reports, PD-L1 positivity are reported to be 50%-80%, although there in inconsistency with its cut-off value [2].

The survival of ENKTL had improved in recent years with intensive chemotherapy including radiotherapy and stem cell transplantation. However, the survival of ENKTL patients who are ineligible for intensive chemotherapy or who have r/r disease remains poor (median survival is around 6 months) [3].

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

Kwong et al. reported the first case series of seven r/r ENKTL patients treated with pembrolizumab, a monoclonal antibody against PD-1 [4]. All patients experienced objective responses to pembrolizumab, including five complete responses (median follow-up, 6 months). This study also suggested that the expression level of PD-L1 assessed by conventional immunohistochemistry could not capture ENKTL patients who may respond to PD-1 blockade therapy. A similar high efficacy of PD-1 blockade were observed in two other studies, in which r/r ENKTL patients were treated with pembrolizumab or nivolumab [5,6]. Currently, several studies are in progress to test the clinical efficacy of PD-1 blockade for ENKTL [NCT03820596].

Kataoka et al. revealed that, in ENKTL, tumor cells frequently had structural variations (SVs) of PD-L1 gene, represented by a truncation of PD-L1 3' UTR, which were the most common genetic alterations [7]. PD-L1 3' UTR is considered to be the non-coding region which plays an important role in the regulation of PD-L1 mRNA expression, controlling PD-L1 mRNA stability, translation efficiency, and localization [8]. They revealed that disruption of PD-L1 3' UTR gives rise to a high expression of PD-L1 transcripts and immune escape. More recently, Lim et al. performed genetic profiling on 19 ENKTL patients who were treated with pembrolizumab and analyzed the relationship between the clinical response and the genetic alterations [9]. They found that a truncation of PD-L1 3' UTR was the only gene alteration which was correlated with response to pembrolizumab, implying that a truncation of PD-L1 3' UTR would be the most powerful biomarker to predict responders to pembrolizumab [9]. However, these findings should be interpreted with caution because the overall response rate (47.3%, 8 out of 19) reported in this study was obviously lower than previous studies [9,10]. Another study reported that ENKTL patients with amplification of PD-L1 locus were more sensitive to PD-1 blockade than patients without PD-L1 amplification [10,11]. Further studies are needed to reveal the role of truncation of PD-L1 3' UTR or PD-L1 amplification as novel biomarkers to predict efficacy of PD-1 blockade among ENKTL patients.

EBV-Positive diffuse Large B-cell Lymphoma, Not otherwise Specified

Overview

EBV-positive diffuse large B-cell lymphoma (DLBCL), NOS is an EBV-positive clonal B-cell lymphoid proliferation, which accounts for 5%-10% of DLBCLs [1]. Morphologically, tumor cells consist of a variable number of large immunoblasts and Hodgkin/Reed-Sternberg-like cells. Cell of origin analysis usually show the activated B-cell type [1]. There is variable component of reactive elements is observed around tumor cells, resembling T-cell/histiocyte-rich large B-cell lymphoma [12]. PD-L1 on tumor cells is positive in more than a half

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 may benefit from ICI therapy, although clinical efficacy of ICI against EBV-positive DLBCL is not elucidated. Recent study showed that pembrolizumab against PD-L1 SVs-positivity may predict the response of pembrolizumab against DLBCL (2 out of 3 with PD-L1 SV responded to pembrolizumab) [19]. Based on these data, clinical trial of pembrolizumab for r/r DLBCL patients with PD-L1 SVs (+) is currently ongoing [NCT39990961]. Thus, subclassification of DLBCL according to genetic alterations, especially for PD-L1 may enable us to capture a fraction of patients who respond to ICI among biologically heterogeneous DLBCLs.

Combining ICIs is an another option to potentiate the efficacy of ICI for DLBCL. Interim results of a phase 1/2 trial of maglolimab, anti-CD47 monoclonal antibody, with rituximab include 46 patients with r/r DLBCL and showed an excellent ORR of 39% with complete remission rate of 20% [NCT02953509]. Combination therapy consisting of CD47-SIRPα blockade and PD-1 blockade will be examined in upcoming clinical trials.

Classical Hodgkin Lymphoma

Overview

CHL is characterized histologically by the presence of Hodgkin and Reed/Sternberg (HRS) cells which derives from germinal center B-cells [1]. Residing near HRS cells, various types of reactive cells are observed, such as tumor associated macrophages (TAMs), CD8-positive T cells, and CD4-positive T cells [1]. Around 40% cases of CHL are associated with EBV infection [1]. Constitutive activation of the NF-kB pathway is frequently observed especially in EBV-positive CHL cases [1]. In addition, copy number alterations (CNAs) of chromosome 9p24.1, containing the loci for PD-L1, PD-L2, and JAK2 are observed in almost all cases of CHL [20]. These genetic abnormalities directly increase PD-L1 expression, while upregulated JAK2 expression and subsequent activation of the JAK/STAT signaling pathway, also enhances the expression of PD-L1 [20]. Front line chemotherapy for CHL are ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for limited disease, and A+AVD (doxorubicin, vinblastine and dacarbazine with brentuximab vedotin) for advanced disease with favorable survival outcomes (OS 80%-95%), however the outcome of r/r CHL remains poor, even after brentuximab vedotin was introduced [21,22].

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

The therapeutic effect of PD-1 inhibitors for CHL is remarkably high, indicating its vulnerability to ICI treatment [23]. Recent pivotal studies reported excellent ORR with ranging 65% to 87% for r/r CHL, and both nivolumab and pembrolizumab were approved by FDA in 2016 [23,24]. On the other hand, the CR rate is relatively low (9%-22%) and the median PFS is short (11-15 months) despite its remarkable ORR, indicating the difficulties of long-term remission with ICI alone [23,24].

Copy number alteration burden of chromosome 9p24.1 is known as a predictive factor for progression free survival (PFS) for the conventional chemoradiotherapy, although there have been no reports about its relationship between the efficacy of PD-1 blockade and CNAs of chromosome 9p24.1 [25].

In CHL, the loss of HLA MHC class II is also observed around 40% of patients, which was caused by CIITA gene rearrangements and somatic mutations, as well as the loss of HLA MHC class I (around 80% of patients) [26-30]. Patients with loss of MHC class II expression were reported to be significantly high number of CD4-positive T cells infiltration in tumor microenvironment [31]. Interestingly, one clinical trial founds that patients with membranous MHC class II expression on HRS cells had significantly better response to nivolumab monotherapy with CR rate of 30% (8 out of 27), compared with patients without MHC class II expression (CR rate 5%, 1 out of 20) [32]. Moreover, the same trial has pointed out that PFS for ICI therapy is significantly longer in patients with positive MHC class II expression than patients with negative MHC class II expression [32]. Furthermore, another study showed that, using xenograft model, PD-1 blockade showed antitumor efficacy as far as MHC class II was positive, irrespective of expression of MHC class I positivity [31]. These results imply that MHC class II and CD4-posotive T-cell axis plays an important role in antitumor effect against PD-1 blockade in CHL, while MHC class I and CD8-positive T-cell axis plays role in solid tumors [31]. Some researchers argue that CD4-positive T cells themselves have antitumor activity against MHC class I-negative/class II-positive tumors by recognizing the MHC class II complexes [31].

LAG3 can be another biomarker to predict the efficacy of ICI therapy [31]. LAG3, one of the immune checkpoint molecules, is expressed on CD4-positive T cells and attenuates the effect of HLA class II mediated antigen presentation competing with CD4-positive T cells by binding to MHC class II [33,34]. Combining anti-LAG3

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) compared to other subtypes of lymphomas [37]. TMB has shown to be a predictive marker for efficacy of ICIs in gastrointestinal cancers [51]. MSI, along with TMB, is also widely used as a predictive biomarker for ability of DNA mismatch repair in solid tumors. Some researchers claim that TMB and MSI will be also biomarkers to predict efficacy of ICI therapy in CHL and PMBL [52]. APOBEC is a cytidine deaminase which causes hypermutations of oncogene and APOBEC mutation signatures are known as a predictive factor for ICI efficacy in NSCLC [53]. APOBEC mutation signatures are also frequently observed in CHL and PMBL, and might be another predictive factor for ICI efficacy in these lymphomas, although further studies are warranted [37].

HIV-related Lymphomas

Overview

Lymphomas that develop in HIV-positive patients are predominantly aggressive lymphomas [1]. The most common HIV-associated lymphomas include Burkitt lymphoma, diffuse large B-cell lymphoma often involving the CNS, primary effusion lymphoma, and plasmablastic lymphoma [1]. Classical Hodgkin Lymphoma (CHL) is also increasing in the setting of HIV infection [1]. EBV infection is sometimes overlapped in the neoplastic cells of approximately 40% of HIV-related lymphomas [1]. Antiretroviral Therapy (ART) for HIV infection has reduced the occurrence of HIV-related lymphomas by 50% and improved overall survival (with a 75% decrease in mortality) [1]. There have been few reports about genetic alterations and gene expression profiles of HIV-related lymphomas, while some reports observed somatic TNFAIP3 mutations and/or chromosome 6q deletion leading to constitutive NK-kappaB activity [54].

ICI for patients with HIV-related lymphomas

Immune checkpoint molecules such as PD-1, LAG3, and TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains) are highly expressed on the surface of the exhausted HIV-specific T-cells, which prompts us to test anti-tumor effects of immune checkpoint inhibitors (ICIs) [55,56]. There has been scarce evidence regarding the efficacy of ICI on HIV-related lymphomas and several questions remains to be unanswered (i.e. potential exacerbation of immune reconstitution inflammatory syndrome when combining ICI and ART).

Primary CNS Lymphoma and Primary Testicular Lymphoma

Overview

Primary CNS lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare types of extranodal B-cell lymphomas that share common clinical and pathological features [17]. Pathologically, they are distinctive subtypes of DLBCL derived from non-GCB B-cells and their TME consists of heterogenous population of cells including B-cells, T-cells, and sometimes histiocytes [1]. Additionally, they shared common genetic signatures in that combined MYD88/CD79B mutations were observed in more than 70% of patients, leading to constitutive NF-kB activation [57]. Moreover, expression of PD-L1 and CNAs of chromosome 9p24.1 are detected in about half of PCNSL and PTL patients (52% in PCNSL and 54% in PTL) [45]. PD-L1 and PD-L2 translocations also have been found in small fraction of PCNSL and PTL cases, 6% and 4%, respectively [45,58]. Prognosis is poor and treatment options are limited for patients with r/r PCNSL or PTL. According to the previous report, the median overall survival of r/r PCNSL is 3.5 months [59].

ICI for patients with HIV-related lymphomas

Retrospective study including 4 patients with r/r PCNSL and 1 patient with r/r PTL treated with nivolumab showed that all 5 patients had clinical responses to nivolumab and 3 patients remained progression-free for more than 12 months [60]. In addition, combination therapy with lenalidomide (immunomodulatory drugs) and ibrutinib (BTK inhibitor) may have synergistic effect [NCT03770416, NCT04462328], considering that each of them has demonstrated notable activity in patients with r/r PCNSL, with objective responses of more than 50% [61-63]. Combing ICI with these small molecules might be reasonable therapeutic options. To date, there has been scarce evidence regarding biomarkers to predict the efficacy of ICI on PCNSL and PTL. Larger clinical trials are needed to examine the clinical efficacy of ICI for PCNSL and PTL.

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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