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Review

Biomarkers for checkpoint inhibition in hematologic malignancies

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ABSTRACT

In the past few years we have seen remarkable paradigm shifts in the treatment of many solid tumors due to the introduction of inhibitors targeting immune checkpoints such as PD-1/PD-L1 and CTLA-4. Recent results indicate that checkpoint inhibition also represents a very promising approach for certain types of hematologic malignancies. Unfortunately, treatment with checkpoint inhibitors is also associated with substantial toxicities and high costs and only a subset of patients appears to derive clinical benefit from these treatments. This demonstrates the urgent need for biomarkers for the identification of patient populations that are likely to respond to this type of therapy and/or have fewer side effects. Here, we have reviewed available information on the prognostic and predictive value of biomarkers for anti-CTLA-4 and anti-PD-1/PD-L1 as the most commonly used checkpoint inhibitors. There are currently no reliable biomarkers capable of predicting responses to anti-CTLA-4 agents, such as ipilimumab, in hematologic malignancies. Certain polymorphisms in the CTLA-4 gene, however, seem to have an impact on the patients' outcome, especially in the case of chronic lymphocytic leukemia (CLL). There is now sufficient data supporting PD-L1 expression levels in the tumor tissue as an independent prognostic factor in B cell lymphomas such as diffuse large B-cell lymphoma (DLBCL). Overexpression of PD-L1 in the tumor tissue and elevated serum levels of soluble PD-L1 may also represent adverse prognostic factors in certain subtypes of T cell lymphomas. Finally, expression levels of PD-L1 also seem to predict responses to anti-PD-1/PD-L1 approaches in patients with Hodgkin lymphoma. Future studies will have to further delineate the prognostic/predictive role of PD-L1 expression as a biomarker in hematologic malignancies and may be able to identify confounding variables, which will hopefully to some extent be generalizable to other types of anti-tumor immunotherapies.

1. Background

In the past few years we have seen remarkable clinical results and complete changes in the treatment algorithms for many solid tumors based on the introduction of inhibitors targeting immune checkpoints such as PD-1/PD-L1 and CTLA-4. For example, in patients with advanced non–small-cell lung cancer (NSCLC), treatment with the PD-1 inhibitor pembrolizumab resulted in significantly longer progression-free (PFS) and overall survival (OS) with fewer adverse events than platinum-based chemotherapy [1]. In the case of advanced melanoma concurrent therapy with both, an anti-PD-1 antibody combined with an anti-CTLA-4 agent, provided clinical activity with rapid and deep tumor regression in a substantial proportion of patients [2].

Unfortunately, treatment with checkpoint inhibitors is also associated with substantial toxicities and high costs and only a subset of patients appears to derive clinical benefit from these treatments. This clearly demonstrates the urgent need for biomarkers for the identification of patient populations that are likely to respond to this type of therapy and/or have fewer side effects. Accordingly, a number of factors have been identified that provide prognostic information and/or are capable of predicting responses to the various checkpoint inhibitors in patients with solid tumors.

PD-L1 expression by immunohistochemistry (IHC) has been used as a predictive biomarker in different solid tumors [3]. One study showed for melanoma that PD-L1 expression in pretreatment tumor biopsy samples correlated with responses to PD-1 checkpoint inhibition as well as PFS and OS [4]. Using a more complex approach, a different group of investigators was able to identify an immune gene signature with predictive value for patients initially treated with CTLA-4 blockade followed by PD-1 inhibition at progression. The gene signature consisted of cytolytic markers, HLA molecules, IFN-γ pathway effectors, chemokines and adhesion molecules. They showed that adaptive immune signatures obtained early during the course of treatment are highly predictive of response to immune checkpoint blockade [5].

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Prognostic and predictive biomarkers have also been identified for solid tumors other then melanoma, e.g. NSCLC. It has been shown that tumors harboring epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements are associated with low overall response rates (ORRs) to PD-1/PD-L1 inhibitors, a phenomenon that may be related to lower PD-L1 expression and numbers of $CD8^+$ tumor-infiltrating lymphocytes (TILs) within the tumor microenvironment [6].

In the case of hematologic malignancies the situation is more complex because clinical responses to immune checkpoint blockade are less common and, accordingly, it has been more difficult to identify reliable predictive biomarkers. In this review we will summarize our current knowledge in the area of hematologic malignancies on the prognostic and predictive value of biomarkers for anti-CTLA-4 and anti-PD-1/PD-L1 as the most commonly used checkpoint inhibitors.

2. CTLA-4

2.1. CTLA-4 expression and its prognostic value in hematologic malignancies

2.1.1. B cell lymphomas

In the case of hematologic malignancies, the majority of the studies on the prognostic/predictive and the therapeutic value of CTLA-4 have focused on B cell lymphomas. For example, it has repeatedly been demonstrated that T cells from patients with chronic lymphocytic leukemia (CLL) show a significantly increased expression of CTLA-4 compared to normal donors [7,8]. Overexpression of CTLA-4 in general has been shown to be associated with a favorable prognosis by some investigators [8].

In agreement with a potential prognostic role of CTLA-4 expression in CLL, it has been shown that blockade of the antigen resulted in enhanced T cell proliferation in response to autologous and allogeneic CD40-activated CLL B cells [7]. Indicating that CTLA-4 expression may be detrimental to the malignant phenotype, Mittal and coauthors knocked down CTLA-4 expression in primary CLL cells but not in T cells from CLL patients and found that CLL cells with CTLA-4 down-regulation demonstrated a significant increase in proliferation and survival along with a decreased frequency of apoptosis and increased expression of Bcl-2 [9].

Other studies have evaluated the prognostic impact of increased levels of soluble CTLA-4 (sCTLA-4) in patients with B cell lymphomas possibly leading to increased T cell inhibition and one study examining 60 patients with de novo acute lymphoblastic leukemia (ALL) observed higher levels of sCTLA4 in patients versus controls and patients who suffered a relapse had significantly higher sCTLA4 levels compared to those who remained in complete remission [10].

Polymorphisms in the CTLA-4 gene are associated with a number of autoimmune diseases including blood disorders and a number of studies have examined the impact of polymorphisms of CTLA-4 on the development of B cell lymphomas. Analyzing the intragenic polymorphisms of the CTLA-4 gene in patients with B cell lymphoma, Monne et al. found that the exon 1 + 49*AA genotype was over-represented among patients suggesting that the CTLA-4 + 49 A/G polymorphism may play role in the genetic susceptibility to B cell lymphomas [11]. Accordingly, Piras et al. analyzed the 2q33 chromosomal region harboring CTLA-4 in 100 lymphoma patients and 128 healthy controls and found a strong association of the CTLA-4 49 A and the 3′-untranslated region $(AT)_{82}$ alleles with lymphoma. CTLA-4-318C:49 A:$(AT)_{82}$ was the most represented haplotype in the studied population and was associated with lymphoma [12]. In patients with CLL an increased frequency of the CTLA4g.319C > T [T] allele and the CTLA4g.319C > T [T] phenotype was observed in patients compared to controls [13].

The presence of CTLA-4 polymorphisms also seems to have a prognostic and predictive value in patients with B cell lymphoma. In CLL patients, the presence of the CTLA4g.319C > T polymorphism was associated with time to Rai stage progression [13]. Quin and coauthors focused on four CTLA-4 polymorphisms (−1661, −318, CT60 and +49) and analyzed the impact of donor genotypes on 152 ALL patients after related HLA-haplotype mismatched transplantation. Recipients of donors with +49 GG showed a significantly lower OS than those with GA + AA. Multivariate analyses showed that +49 GG was an independent risk factor for OS. The 23 ALL patients receiving DLI showed a significantly lower OS with a +49 GG donor than those with a GA + AA donor [14].

Overall, several strategies, such as CTLA-4 expression and polymorphisms in the CTLA-4 gene, appear to be correlated with response to CTLA-4 inhibition in B cell lymphomas. However, none of these strategies have been confirmed in prospective clinical studies and the clinical utility, especially of individual CTLA-4 polymorphisms as a predictive biomarker, remains uncertain.

2.1.2. T cell lymphomas

Only comparably few studies have examined the role of CTLA-4 in T cell lymphomas. In one initial study, tumor cells isolated from the skin or peripheral blood of patients with adult T cell leukemia/lymphoma (ATL) showed strong expression of CTLA-4 [15]. In another study looking at the mRNA expression of CTLA-4 in peripheral blood cells from 28 patients with leukemic cutaneous T cell lymphoma only 21% of the patients expressed the immune checkpoint and its expression did not have a significant impact on the patients' prognosis [16].

2.1.3. Hodgkin lymphoma

More than 20 years ago Delabrie and coauthors evaluated the expression of the CTLA-4 ligand CD80 in lymph nodes affected by Hodgkin lymphoma (HL). The ligand was found to be strongly expressed by the Reed-Sternberg cells in all cases of HL studied and the Reed-Sternberg cells were frequently surrounded by CD28-expressing T cells. Importantly, in an allogeneic mixed lymphocyte reaction using HL-derived cell lines as stimulators, proliferation and cytokine production by T cells could be partially blocked by adding an anti-CD80 monoclonal antibody, suggesting an accessory cell function of CD80-expressing Reed-Sternberg cells in HL [17]. A few years later, strong expression of CTLA-4 was reported on the tumor-infiltrating lymphocytes, but not Reed-Sternberg cells, of the vast majority of patients with HL as well as on the neoplastic cells of most patients with T cell malignancies and Vandenborre and coauthors confirmed expression of CTLA-4 on T cells infiltrating HL lesions [18].

HL-infiltrating $CTLA\text{-}4^+$ T cells appear to have an immunosuppressive function [19] and are impacted by the remission status of the patient as the mean percentage of CTLA-4+ T cells from patients in clinical remission (CR) was lower than that of untreated patients, but remained significantly higher compared to controls. The proportion of CTLA-4 T cells negatively correlated with proliferative activity and cytokine production in HL patients and controls [20].

2.1.4. Myeloid leukemias

A number of studies have analyzed the effect of polymorphisms of the CTLA-4 gene on the outcome of patients with myeloid leukemias after stem cell transplantation. The single-nucleotide polymorphism CT60, located in the 3′-untranslated region of the CTLA-4 gene, has been associated with susceptibility to several autoimmune diseases and has also been shown to be involved in immune responses following allogeneic stem cell transplantation (alloSCT). Perez-Garcıa and coauthors investigated the association between the CTLA4 CT60 A/G genotype and the incidence of leukemic relapse in 143 adult patients with acute myeloid leukemia (AML) in first complete remission. The CT60 AA genotype was found to be associated with a higher rate of leukemic relapse and lower OS at 3 years [21]. In a different study, multivariable analysis adjusting for relevant donor and recipient characteristics showed no significant association between AG and GG genotypes of donor CTLA-4 single nucleotide polymorphism (SNP)