Editorial

Will PD-1/PD-L1 Inhibitor Become a True Salvage Therapy for Relapsed or Refractory Patients with Hematological Malignancies?

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Introduction

The treatment of cancer has evolved tremendously with the advent of immunotherapy. The effort of several groups in 1990’s led to the discovery that cancer cells use a specific mechanism called the Programmed death-1 pathway to evade the host immune response [1]. Since then, several drugs and clinical trials have been designed that either block the receptor PD-1 or its ligand PD-L1. Recent approval of four different PD-1/PD-L1 inhibitor drugs avelumab, pembrolizumab, nivolumab and atezolizumab in different solid tumors have established PD-1 inhibition as a promising pathway in other cancers [2-5].

The primary option for relapsed or refractory patients with hematological malignancies and who is ineligible to hematopoietic stem cell transplantation is chemotherapy. However, poor response, poor overall survival benefit and long term side effects seen with chemotherapy arises a dire need for identification of specific targeted therapy in these patients as well [6]. The draft versus leukemia or lymphoma effect observed on lymphocyte infusion as well as established therapies against CD20 and CD30 antigens highlights the ability of immune response to kill cancer cells [7,8]. The recent approval of nivolumab and pembrolizumab in classical Hodgkin’s lymphoma as well as the expression of PD-1 in several different hematological malignancies establishes PD-1 checkpoint inhibitors as a potential therapy for relapsed or refractory hematological malignancies [9,10]. However, the lower response rate of PD-1 inhibitors in different hematological malignancies compared to cHL, the unique biology of cHL enabling better response in this disease group as well as the growing number of clinical trials with bispecific antibodies and chimeric antigen T-cell receptors could hinder the development of PD-1 inhibitors as the dominant salvage therapy in this relapsed or refractory hematological malignancies [9-16]. In the end, the therapy that shows highest benefit will become the mainstay for salvage therapy.

Discussion

Evasion of the host immune response is one of the main hallmarks in the development of cancer [17]. Programmed Death-1 pathway is emerging as a major pathway in evading immune response. This pathway mainly includes the Programmed death-1 receptor (PD-1), which is expressed on the surface of progenitor T-cells, activated T and B-lymphocytes, natural killer cells and myeloid cells. On binding to its ligands PD-L1 and PD-L2, the receptor activates the down-regulation of T-cell receptor signaling, which ultimately leads to apoptosis of activated T cells [6,18,19]. Inactivation of this pathway by PD-1/PD-L1 inhibitors prevents the tumor cells from immune evasion and helps impede tumor progression.

Immune checkpoint inhibitors, having demonstrated superior clinical efficacy over chemotherapy are looking more and more promising to become the primary standard of care across multiple different solid tumors. Recent approvals of avelumab, pembrolizumab, nivolumab and atezolizumab in different solid tumors including merkel cell carcinoma, Non-Small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma (RCC), Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma and Urothelial carcinoma further proves that PD1/PD-L1 is set to become the backbone therapy in multiple solid tumors [5,11,16,20].

The ability of immune response to kill cancer cells has been widely demonstrated in hematological malignancies through graft versus leukemia or lymphoma (GVL) effect seen upon transplantation and lymphocyte infusion [7,8], as well as through established therapies against hematological markers CD20 and CD30. Despite the proven benefit of anti-tumor immune response in hematological malignancies, these cancers have garnered very little attention as a target for PD-1/PD-L1 therapy, compared to the solid tumors. Expression of PD-1 pathway in various hematologic malignancies ranging from angioimmunoblastic T-cell lymphoma (AITL), anaplastic large T-cell lymphoma (ALCL), acute myeloid leukemia (AML), adult T-cell leukemia/lymphoma (ATL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Hodgkin’s lymphoma (HL), human T-lymphotropic virus-1 (HTLV-1), nodular lymphocyte predominant Hodgkin’s lymphoma (NHL-PH), plasma cell myeloma (PCM), primary mediastinal B-cell lymphoma (PMBCL) and small lymphocytic lymphoma (SLL) have been observed [4]. Over the years, chemotherapy has been the primary treatment option for patients with relapsed or refractory hematological malignancies that are ineligible or have not benefited from hematopoietic stem cell transplantation (HSCT). With multiple PD-1/PD-L1 inhibitors currently being tested in clinical trials, there is a possibility of PD-1/PD-L1 inhibitors creating a niche across these cancer subtypes [6,21].

Recent accelerated approvals of Pembrolizumab and Nivolumab in classical Hodgkin’s Lymphoma (cHL) presents a promising alternative to chemotherapy in relapsed or refractory patients with hematological malignancies [2,5,11,20]. Nivolumab approval was based on the results reported from Phase-1 (CheckMate-039) and Phase-2 (CheckMate-205) trials. The results of Phase I trial assessed the therapeutic activity of nivolumab in patients with previously heavily treated relapsed or refractory Hodgkin’s lymphoma. The study observed an overall response rate (ORR) of 87% with complete response (CR) of 17% (4 patients) and partial response (PR) of 70% (16 patients). Combined results of Phase-2 and Phase-1 trial reported an ORR of 65% (62/95 patients) with 17% CR (7/95 patients) and 58% PR (55/95 patients). The median response duration was 8.7
months. Accelerated approval of Phase-II pembrolizumab trial (KEYNOTE-087) of 210 patients reported results with ORR of 69% (62/75), CR of 22% and PR of 47%. The median response duration of 11 months was reported [20].

Despite the accelerated approvals for pembrolizumab and nivolumab in cHL, it remains to be seen whether PD-1/PD-L1 inhibitors will be able to extend their use in other hematological malignancies too. There are several potential risks for PD-1/PD-L1 inhibitors becoming the standard salvage therapy in other relapsed or refractory hematological malignancies. It is known that there is a variable PD-1 expression across different lymphomas [9,10]. In addition, results from Lesokhin et al. showed ORR of 40%, 36%, 15% and 40% among nivolumab treated patients with follicular lymphoma, diffuse large B-cell lymphoma, mycosis fungoides and peripheral T-cell lymphoma respectively [22]. The weaker ORR compared to that seen in cHL could imply that the success and use of PD-1/PD-L1 could become restricted to cHL. cHL is a unique B-cell malignancy, wherein the rare Reed-Sternberg (RS) cells are present along with surrounding immune microenvironment. Chromosomal abnormality by 9p24.1 gene amplification and Epstein-Barr infection leads to high expression of PD-L1 on RS cells. PD-L1 on RS cells binds to PD-1 present on the immune effector cells, which in turn helps in immune evasion, ultimately leading to cancer growth and progression [11,13-15]. A recent study by Godfrey et al. in a very small number of patients showed the benefit of nivolumab treatment following allogeneic transplant in Hodgkin’s lymphoma patient [12]. Despite the report, it would be very difficult to see PD-1/PD-L1 inhibitors being used in patients that have undergone allogeneic HSCT transplantation due to significant risk of developing graft-versus-host-disease (GVHD), febrile syndrome, hepatic veno-occlusive disease and other immune mediated adverse reactions [2,3].

Furthermore, the growing numbers of clinical trials of bispecific antibodies and Chimeric Antigen Receptor (CAR) T-cells in relapsed or refractory hematological malignancies will pose a competitive threat to PD-1/PD-L1 inhibitors use in this space [16]. The trial results will determine if there would be a preferred standard of care that could displace chemotherapy from being the current salvage treatment in these patients. A possibility could also arise where based on expression of different markers; there is a place for multiple different immune-oncology therapies to co-exist. PD-1/PD-L1 inhibitors would have to create a defined therapeutic rationale and a unique differentiation strategy from its competition to form a niche in the relapsed or refractory patients with hematological malignancies. With the rapid advancement of the immune-oncology space, there is a strong expectation associated with these therapies to be efficacious, cost-effective, provide better quality of life and most importantly improved survival for the patients whose primary option currently is chemotherapy.

References
1. Dana-Farber Cancer Institute (2017) what is the Science of PD-1 and Immunotherapy?.