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Avelumab

Updated: July 20, 2017.

OVERVIEW

Introduction

Avelumab is a human monoclonal antibody to programmed cell death receptor ligand 1 (PD-L1), which modulates T cell immune reactivity and is used in the immunotherapy of cancer. Avelumab has major side effects and particularly immune related conditions, including acute liver injury which can be serious and even life threatening.

Background

Avelumab (av el' ue mab) is a human recombinant monoclonal IgG1 antibody to the programmed cell death receptor ligand-1 (PD-L1) which has distinctive immunomodulatory activity and is used in cancer immunotherapy. PD-1 is an important checkpoint molecule that modulates and down regulates T cell responses. Antibody binding to the ligand prevents its binding to the programmed cell death receptor which thereby allows for a continued activation and proliferation of T cells. The subsequent enhancement of cytotoxic reactivity may play a beneficial role in cancer immunotherapy by breaking immunological tolerance to cancer cell neo-antigens. In several multicenter studies, avelumab therapy resulted in objective responses in patients with advanced, metastatic or unresectable malignant neoplasms, and a proportion of patients had a long term remission. Avelumab was approved for use in metastatic Merkel cell carcinoma and advanced, refractory urothelial bladder carcinoma in the United States in 2017, and is currently under evaluation in several other forms of cancer, including NSCLC. Avelumab is available in single use 10 mL vials of 200 mg (20 mg/mL) under the brand name Bavencio. The recommended dose is 2 mg/kg as an intravenous infusion every 2 weeks. Premedication with acetaminophen and antihistamines is recommended for the first 4 infusions. Side effects are common and include fatigue, nausea, musculoskeletal pain, rash and infusion reactions. Between 5% and 20% of treated patients develop immune related side effects as a result of immune enhancement including enterocolitis, dermatitis, endocrinopathy, pneumonitis, neuropathy, nephritis and hepatitis. Most of these reactions respond to dose interruption and/or immunosuppressive therapy, but some have resulted in fatalities and some have required long term therapy. Early recognition and prompt management of these side effects is an integral component of proper use of checkpoint inhibitors such as avelumab.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not common (~1% to 4%) during avelumab therapy, but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 0.5% to 1.5% of patients, and a proportion of these individuals develop clinically apparent liver injury that can be severe. The onset of such injury is usually after 2 to 6 cycles or

1 to 3 months after initiation of treatment. The pattern of enzyme elevation is usually hepatocellular. Monitoring of serum enzymes is recommended with dose interruption for values above 3 times the ULN and discontinuation for values above 5 times the ULN. When serum aminotransferase levels remain elevated despite discontinuation or with development of symptoms or jaundice, early intervention with immunosuppressive therapy is prudent and generally results in rapid resolution. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Autoantibodies are usually not present and immunoglobulin levels may not be elevated. Restarting avelumab can result in recurrence of injury, although corticosteroid treatment may block recurrence. Immune mediated hepatitis appears to be more frequent with anti-CTLA-4 than with anti-PD1 or anti-PD-L1 checkpoint inhibitors.

The effects of PD-L1 inhibition on chronic hepatitis B have not been reported as enrollment criteria in the clinical trials of avelumab, which have usually excluded patients with chronic viral hepatitis. However, it is likely that anti-PD-L1 treatment would exacerbate chronic hepatitis B by enhancing T cell cytotoxicity to viral antigens. Interestingly, checkpoint immunotherapy has not been found to be deleterious in patients with chronic hepatitis C and in some cases resulted in a decrease in viral levels.

Likelihood score: E* (although no avelumab related cases of clinically apparent immune mediated hepatitis have been described in the literature, this is a relatively recently approved medication and is likely to be a cause of clinically apparent acute liver injury).

Mechanism of Injury

The mechanism of liver injury due to avelumab is likely to be immunologically mediated and many cases of checkpoint related, immune mediated hepatitis have appeared to respond to corticosteroid or immunosuppressive therapy allowing for continuation or restarting of therapy.

Outcome and Management

Guidelines for management of patients receiving avelumab recommend monitoring of liver tests and interrupting therapy for patients who develop persistent serum aminotransferase elevations above 3 times the ULN and discontinuing treatment for values above 5 times the ULN. Corticosteroid therapy can be considered for patients with persistent ALT elevations or if symptoms or jaundice arise, initiating therapy with high dose intravenous methylprednisolone and switching to oral prednisone after 1 to 2 days, continuing tapering doses for at least 30 days. Most cases of hepatitis due to checkpoint inhibitors resolve with prompt institution of immunosuppressive therapy. The few fatal cases that have been reported during immunotherapy with checkpoint inhibitors occurred in patients who had other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome) or who had a delay in starting corticosteroid therapy. Patients with immune related adverse events due to avelumab can frequently restart therapy once the adverse event has resolved, although concurrent immunosuppressive therapy may be necessary.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies, Checkpoint Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Avelumab – Bavencio®

DRUG CLASS

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Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Avelumab	1537032-82-8	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2017

Abbreviations used: CTLA-4, cytotoxic T lymphocyte associated antigen 4; PD-L1, programmed cell death receptor ligand-1; NSCLC, non-small cell lung cancer.

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, Restifo NP, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A 2003; 100: 8372-7. PubMed PMID: 12826605.

(Initial study of anti-CTLA-4 therapy in 14 patients with melanoma, 6 of whom developed clinically apparent immune adverse reactions, including one with hepatitis arising after the third infusion [ALT 6820 U/L], resolving over the ensuing 4 months with corticosteroid therapy: Case 1).

Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012; 57: 2233-40. PubMed PMID: 22434096.

(Clinical and histological features of 5 patients with acute liver injury due to ipilimumab; 3 men and 2 women, ages 43 to 76 years, arising after 2-4 courses, 39-71 days after initial dose [peak bilirubin 1.5-5.1 mg/dL, ALT 326-3070 U/L, Alk P 206-427 U/L], only one had autoantibodies, resolving with immunosuppressive therapy within 1-4 months; one had recurrence on rechallenge; liver biopsies showed acute hepatitis usually with prominent inflammation, interface hepatitis and confluent necrosis: Case 1 Ipilimumab).

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-54. PubMed PMID: 22658127.

(Among 296 patients with advanced cancers [melanoma, NSCLC, renal, prostate and colorectal] treated with 1 of 5 doses of nivolumab every 2 weeks, response rates were highest with melanoma and renal cancer, and drug related adverse events were common, including immune related conditions such as pneumonitis [3 fatal], vitiligo, colitis, hepatitis [reversible in all cases], hypophysitis and thyroiditis; ALT elevations occurred in 11 patients [4%] and were greater than 5 times ULN in 2 [1%]).

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366: 2455-65. PubMed PMID: 22658128.

(Among 207 patients with various advanced solid tumors treated with an anti-PD-L1 monoclonal antibody daily for 14 days in 6 week cycles for an average of 12 weeks, durable tumor regression occurred in 6-17% of patients; serious adverse events considered related to therapy occurred in 5%, but no patient had ALT elevations above 5 times ULN).

Teply BA, Lipson EJ. Identification and management of toxicities from immune checkpoint-blocking drugs. Oncology (Williston Park) 2014 Nov; 28 Suppl 3: 30-8. PubMed PMID: 25384885.

(Clinical review of the toxicities of immune checkpoint blocking drugs such as ipilimumab, pembrolizumab and nivolumab; mentions that elevations of serum aminotransferase elevations should lead to careful exclusion of other causes of liver injury and increased monitoring; that elevations above 3 times ULN should lead to withholding the drug and starting corticosteroids; that elevations above 5 times ULN should lead to hospital admission and immediate administration of high doses of corticosteroids).

Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014 Nov 27; 515 (7528): 568-71. PubMed PMID: 25428505.

(Analysis of expression of PD-1 and its ligand on CD8+ T cells at the margins of melanoma tumors before and after treatment with pembrolizumab showed that high levels of PD-1 and its ligand are found in responders to therapy).

Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015; 348 (6230): 56-61. PubMed PMID: 25838373.

(Commentary and review of the rationale, history, clinical efficacy and mechanism of action of immune checkpoint therapy).

Abdel-Rahman O, El Halawani H, Fouad M. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Expert Opin Drug Saf 2015; 14: 1507-18. PubMed PMID: 26394770.

(Analysis of publications on checkpoint inhibitors indicate that therapy is associated with higher rates of ALT elevations).

Davar D, Wilson M, Pruckner C, Kirkwood JM. PD-1 blockade in advanced melanoma in patients with hepatitis C and/or HIV. Case Rep Oncol Med 2015; 2015: 737389. PubMed PMID: 26448890.

(59 year old woman and 47 year old man with metastatic melanoma and combined HIV and hepatitis C infection were treated with pembrolizumab, tolerating therapy with no worsening of liver disease or HIV infection).

Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016; 17: 1374-85. PubMed PMID: 27592805.

(Among 88 patients with chemotherapy refractory Merkel cell carcinoma treated with avelumab [10 mg/kg intravenously every 2 weeks], 28 [32%] developed an objective response including 8 with a complete response, and side effects were common including one patient with ALT elevations above 5 times ULN and one death due to hepatic failure; no details provided).

Apolo AB, Infante JR, Balmanoukian A, Patel MR, Wang D, Kelly K, Mega AE, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol 2017; 35: 2117-24. PubMed PMID: 28375787.

(Among 44 patients with refractory urothelial bladder cancer treated with avelumab, 5 had a complete and 3 a partial response, and adverse reactions included fatigue [32%], infusion reactions [21%], and nausea [11%]; while ALT or AST elevations occurred in 3 patients, only one was above 5 times ULN in whom avelumab was discontinued early).

Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, Lamping E, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017; 18: 587-98. PubMed PMID: 28373007.

(Among 53 patients with various refractory solid tumors treated with 1 of 4 doses of avelumab every 2 weeks, common side effects were fatigue, flu-like symptoms and fever, and 3 developed autoimmune disorders, one with ALT elevations above 5 times ULN).

Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, Leach J, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Onco. 2017; 18: 599-610. PubMed PMID: 28373005.

(Among 184 patients with refractory NSCLC treated with avelumab [10 mg/kg every 2 weeks], 22 [12%] had an objective response, but side effects were frequent with immune related events occurring in 22 [12%], although none were liver related).

Kotsakis A, Georgoulias V. Avelumab, an anti-PD-L1 monoclonal antibody, shows activity in various tumour types. Lancet Oncol 2017; 18: 556-557. PubMed PMID: 28373006.

(Commentary on Gulley [2017] and the promise of avelumab in NSCLC).

In brief: Avelumab (Bavencio) for metastatic merkel cell carcinoma. Med Lett Drugs Ther 2017; 59 (1521): e120. PubMed PMID: 28699934.

(Concise review of the mechanism of action, efficacy, safety and costs of avelumab shortly after its approval in the US as therapy of metastatic Merkel cell carcinoma).

Kim ES. Avelumab: first global approval. Drugs 2017; 77: 929-37. PubMed PMID: 28456944.

(Review of the mechanism of action, pharmacology, clinical efficacy and adverse events of avelumab shortly after its approval for use in Merkel cell carcinoma in the US; mentions that one patient of 88 with Merkel cell cancer developed ALT elevations above 5 times ULN which resolved when avelumab was discontinued, and that there were no deaths that were considered treatment related).