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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Pembrolizumab. [Updated 2016 May 1].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Pembrolizumab

Updated: May 1, 2016.

OVERVIEW

Introduction

Pembrolizumab is a humanized monoclonal antibody to programmed cell death receptor 1 (PD-1), which results in an increased immune reactivity that can break tolerance and is used in the immunotherapy of cancer. Pembrolizumab therapy has many adverse events and particularly immune related conditions, including acute hepatitis and acute liver injury which can be serious and even life threatening.

Background

Pembrolizumab (pem" broe liz' ue mab) is a humanized recombinant monoclonal IgG4 kappa-isotype antibody to the programmed cell death receptor-1 (PD-1) 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. Inhibition of PD-1 receptors on the surface of activated T cells prevents their binding to the PD ligand which ordinarily terminates the activation and proliferation of T cells. Without the PD-1 receptor engagement, T cell responses remained activated. 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 large multicenter studies, pembrolizumab therapy resulted in a prolongation of survival in patients with advanced, metastatic or unresectable malignant melanoma, and a proportion of patients had a long term remission. Pembrolizumab was approved for use in advanced melanoma in the United States in 2014 and for advanced non-small cell lung cancer (NSCLC) in 2015. It is also under active investigation in several other forms of cancer, including breast and renal cancer and lymphomas. Pembrolizumab is available in single use vials both as a powder for reconstitution and as a liquid solution (25 mg/mL) under the brand name Keytruda. The typical regimen is 2 mg/kg as an intravenous infusion every 3 weeks. Side effects are common and can be severe. As many as half 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 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 pembrolizumab.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon (~10%) during pembrolizumab 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 and early intervention with immunosuppressive therapy generally results in rapid resolution. However, without treatment the abnormalities can progress to clinically apparent liver injury with jaundice. 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 pembrolizumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

The effects of PD-1 inhibition on chronic hepatitis B have not been reported as enrollment criteria in the clinical trials of pembrolizumab have usually excluded patients with chronic viral hepatitis. However, it is possible that anti-PD-1 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 specific cases have been described in the literature, this is a relatively recently approved medication and is likely to be a not uncommon cause of clinically apparent acute liver injury).

Mechanism of Injury

The mechanism of liver injury due to pembrolizumab is likely to be immunologically mediated and some cases have appeared to respond to corticosteroid or immunosuppressive therapy, allowing for continuation or restarting of pembrolizumab therapy.

Outcome and Management

Guidelines for management of patients receiving pembrolizumab recommend monitoring of liver tests and use of corticosteroids for patients who develop serum aminotransferase elevations above 5 times the ULN, 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 pembrolizumab 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 pembrolizumab 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

Pembrolizumab – Keytruda®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pembrolizumab	1374853-91-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 01 May 2016

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 nivolumab given 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).

Gardiner D, Lalezari J, Lawitz E, DiMicco M, Ghalib R, Reddy KR, Chang KM, et al. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLoS One 2013; 8: e63818. PubMed PMID: 23717490.

(Among 56 patients with chronic hepatitis C treated with a single injection of nivolumab or placebo, decreases in HCV RNA occurred in 11% of both groups, 12% had immune related adverse events and one a transient ALT elevation above 10 times ULN).

Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet 2014; 384 (9948): 1109-17. PubMed PMID: 25034862.

(Among 173 adults with advanced metastatic melanoma not responding to ipilimumab treated with pembrolizumab [2 or 10 mg/kg every 3 weeks], objective response rates were 26% at both doses; ALT elevations occurred in 3.5% of patients, but were below 5 times ULN; one patient developed "autoimmune hepatitis", but no further information provided).

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; and, 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; 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).

Pembrolizumab (Keytruda) for metastatic melanoma. Med Lett Drugs Ther 2014; 56 (1455): e114-5. PubMed PMID: 25538981.

(Concise review of the rationale, mechanism of action, efficacy, safety and cost of pembrolizumab as therapy for metastatic melanoma shortly after its approval in the US; mentions that immune related adverse events occur, but are uncommon and can include hepatitis).

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348 (6230): 124-8. PubMed PMID: 25765070.

(Exome sequencing from NSCLC tumors in patients treated with pembrolizumab showed that patients with a durable clinical benefit of therapy typically had higher numbers of nonsynonymous mutations, an association confirmed in a second cohort; mutations were not in the known PD-1 or checkpoint pathways, but likely represented genes that express neo-antigens).

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).

Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother 2015; 64: 765-7. PubMed PMID: 25828465.

(54 year old woman with melanoma who was treated unsuccessfully with nivolumab and ipilimumab, developed diabetic ketoacidosis after 3 doses of pembrolizumab [anti-GAD positive] having had normal glucose levels before treatment, but also having high risk HLA alleles for type 1 diabetes; no mention of ALT elevations).

Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, Herold KC. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 2015; 38: e55-7. PubMed PMID: 25805871.

(Description of 5 patients with cancer who had new-onset of insulin dependent diabetes 1 week to 5 months after starting nivolumab [n=4] or pembrolizumab [n=1], 3 with anti-GAD, and all requiring insulin therapy chronically; 3% of patients treated with these agents at this cancer center).

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, et al.; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 20155; 372: 2521-32. PubMed PMID: 25891173.

(Among 834 patients with advance melanoma treated with pembrolizumab [Pem: 10mg/kg every 2 or 3 weeks] or ipilimumab [Ipil: 3 mg/kg every 3 weeks], 6 month progression free survival was higher with Pem [47% and 46%] than Ipil [26.5%] and adverse events were less; thyroiditis was more common with Pem, whereas colitis and hypophysitis were more common with Ipil; ALT elevations occurred in 3% [Pem] vs 3.5% [Ipil] and were above 5 times ULN in 0.2% vs 0.8%).

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, et al.; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018-28. PubMed PMID: 25891174.

(Among 495 patients with advanced NSCLC treated with pembrolizumab in 1 of 3 dose regimens, the overall response rate was 19% but was higher among those with greater PD-ligand 1 staring of tumor cells; adverse events occurred in 71%, including hypothyroidism 7%, pneumonitis 4% [1 fatal], and ALT elevations 2.2%).

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509-20. PubMed PMID: 26028255.

(Among 41 patients with advanced cancers with or without mismatch repair deficiency, response rates to pembrolizumab were higher in those with mismatch repair deficiency [53%] than in those without [0%]; adverse events occurred in 98% of patients; ALT elevations occurred in 3 [7%] patients and were greater than 5 times ULN in 2 [5%]).

Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015; 16: 908-18. PubMed PMID: 26115796.

(Among 540 patients with advanced ipilimumab-refractory melanoma treated with pembrolizumab [2 or 10 mg/kg every 3 weeks] or standard chemotherapy, progression free survival at 6 months was greater with pembrolizumab and adverse events were less; ALT elevations occurred in 4 patients [1.1%] and were greater than 5 times ULN in 1 [0.3%]).

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 indicated that therapy was 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).