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Durvalumab

Updated: July 20, 2017.

OVERVIEW

Introduction

Durvalumab is a human monoclonal antibody to programmed cell death receptor ligand 1 (PD-L1), which results in an increased immune reactivity which can break tolerance and is used in the immunotherapy of cancer. Durvalumab therapy has many adverse events and particularly immune related conditions, including acute liver injury which can be serious and even life threatening.

Background

Durvalumab (dur val" ue mab) is a human recombinant monoclonal IgG1 kappa-isotype antibody to the ligand for programmed cell death receptor-1 (PD-L1) which leads to enhanced T cell responses against cancer cells and is used in cancer immunotherapy. PD-1 is an important checkpoint molecule that modulates and down regulates T cell responses. Inhibition of the PD-L1 prevents its binding to the programmed cell death receptor 1 which is responsible for down regulating T cell responses. Inhibition of this pathway 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 large multicenter studies, durvalumab therapy resulted in a prolongation of survival in patients with advanced, metastatic or unresectable urothelial carcinoma, and a proportion of patients had a long term remission. Durvalumab was approved for use in advanced urothelial cancer in the United States in 2017 and it continues to be assessed for efficacy in several other solid tumors and lymphomas including advanced non-small cell lung cancer (NSCLC). Durvalumab is available as a solution in single use vials of 120 and 500 mg (50 mg/mL) under the brand name Imfinzi. The typical regimen is 10 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or intolerance. Side effects are common and can be severe. Common adverse reactions include fatigue, musculoskeletal pain, constipation, anorexia, nausea, and peripheral edema. 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 avelumab.

Hepatotoxicity

In the preregistration clinical trials of durvalumab, mild-to-moderate serum aminotransferase elevations were not uncommon (~10%), although most abnormalities were self-limited and resolved even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occurred in 0.5% to 1.5% of

patients, and a proportion of these individuals develop clinically apparent liver injury that was severe in some instances. The onset of such injury was usually after 2 to 6 cycles or 1 to 3 months after initiation of treatment. The pattern of enzyme elevation was usually hepatocellular. For this reason, 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 durvalumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

The effects of PD-L1 inhibition on chronic hepatitis B have not been reported as enrollment criteria in the clinical trials of durvalumab 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: C (although no specific cases have been described in the literature, 4 cases of immune mediated hepatitis were described in the FDA review of durvalumab; the incidence of hepatitis in the preregistration studies was 1% and clinically apparent injury occurred despite careful monitoring and regimens of dose interruption and discontinuation based upon monitoring of liver tests every 2 to 4 weeks).

Mechanism of Injury

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

Outcome and Management

Guidelines for management of patients receiving durvalumab recommend monitoring of liver tests at the time of the infusions for the first 4 cycles and then monthly thereafter and as clinically indicated. Most cases of hepatitis due to durvalumab 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 durvalumab 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

Durvalumab – Imfinzi®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

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Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Durvalumab	1428935-60-7	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 one; 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 [anti-CTLA-4]; 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%]).

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 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).

Syed YY. Durvalumab: First global approval. Drugs 2017; 77 (12): 1369-76. Erratum in: Drugs. 2017 Oct 10. PubMed PMID: 28643244.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of durvalumab shortly after its approval for use in metastatic urothelial carcinoma in the US; mentions that liver injury occurred in 3.3% of patients and fatalities of acute liver injury have occurred).

Three drugs approved for urothelial carcinoma by FDA. Cancer Discov 2017; 7: 659-60. PubMed PMID: 28546286.

(News report on the approval of 3 new checkpoint inhibitors for therapy of advanced or metastatic urothelial carcinoma in patients whose disease has advanced despite treatment with platinum-containing chemotherapies: pembrolizumab [anti-PD1], avelumab [anti-PD-L1] and durvalumab [anti-PD-L1]).

Massard C, Gordon MS, Sharma S, Rafi S, Wainberg ZA, Luke J, et al. Safety and efficacy of durvalumab (MED 14736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016; 34: 3119-25. PubMed PMID: 27269937.

(Among 41 patients with advanced, refractory urothelial bladder cancer treated with durvalumab for up to 12 months, the objective response rate was 31% and adverse event rate 64%; most frequently fatigue [13%], diarrhea [10%] and anorexia [8%]; no mention of ALT elevations or hepatotoxicity).

Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, Narwal R, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol 2016; 17: 299-308. PubMed PMID: 26858122.

(Among 102 patients with refractory NSCLC treated with various doses of durvalumab [anti-PD-L1] and temelimumsb [anti-CTLA-4], side effects were common leading to discontinuations in 28% and ALT elevations in 0% to 12% of regimens).

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761069Orig1s000MedR.pdf.

(Summary of FDA review of safety of durvalumab including descriptions of cases of immune mediated hepatitis, one of which was fatal: pages 74-9).