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Aldesleukin

Updated: May 5, 2018.

OVERVIEW

Introduction

Aldesleukin is a recombinant form of human interleukin-2, a cytokine that stimulates the proliferation and maturation of T cells, which is used in immune therapy of renal cell cancer and malignant melanoma. When given in high doses, interleukin-2 regularly causes mild-to-moderate elevations in serum enzymes and bilirubin, but it rarely results in clinically significant acute liver injury.

Background

Aldesleukin (al" des loo' kin) is recombinant form of interleukin-2 (IL-2), a human cytokine produced by macrophages and lymphocytes that induces the proliferation and maturation of T cells. Also known as T cell growth factor, interleukin-2 is a critical cytokine in the adaptive immune process and interacts with specific T cell receptors to activate intracytoplasmic pathways that lead to proliferation and differentiation of immature T lymphoblasts into mature and reactive T cells that play an important role in immune responses to foreign proteins, viruses and bacteria and tumor cells. A recombinant form of interleukin-2 has been developed and shown to be an immune modulator and to have antitumor activity against several malignancies, but most convincingly renal cell cancer and malignant melanoma. Aldesleukin was approved for use in the United States for malignant melanoma in 1992 and indications were subsequently broadened and now include metastatic renal cell carcinoma and metastatic malignant melanoma. Aldesleukin is available as lyophilized powder in vials of 22 million IU under the brand name Proleukin. The typical dose is 600,000 IU/kg intravenously every 8 hours for a maximum of 14 doses, which can be repeated after a 9 day rest depending upon tolerance. Side effects are common, particularly with high dose interleukin-2 which should be administered in a hospital setting under the supervision of physicians experienced in the use of anticancer agents. Common side effects include fatigue, fever, chills, nausea, diarrhea, and capillary leak syndrome which can cause peripheral edema, hypotension, renal insufficiency and pulmonary edema. Less common, but potentially severe adverse reactions include shock, anaphylaxis, severe infections, autoimmune conditions and neurologic complications including somnolence, stupor and coma.

Hepatotoxicity

In multiple phase 2 and 3 clinical trials, interleukin-2 was found to cause mild-to-moderate serum enzyme elevations in at least half of patients receiving intravenous therapy for malignancies. These elevations were generally transient and without obvious symptoms of liver injury, but rose to levels above 5 to 10 times ULN and necessitated early discontinuation or delay in further therapy in some patients. Extended courses of high dose interleukin-2 commonly lead to cholestasis, with increases in serum bilirubin and bile acids within 5 to 7 days of

starting therapy followed by rises in alkaline phosphatase and aminotransferase levels. These changes reverse rapidly with discontinuation. The general pattern of bilirubin and enzyme elevations in these studies resembled the jaundice of sepsis or benign postoperative cholestasis and suggested a direct effect of IL-2 on bile and bile salt transport and secretion. With currently recommended doses given for 5 days these effects are less evident. In addition, instances of idiosyncratic clinically apparent acute liver injury with jaundice attributable to aldesleukin therapy have not been reported, although the product label mentions "hepatitis" as a potential complication of therapy. Thus, interleukin-2 has been clearly linked to serum enzyme elevations and cholestasis during treatment, but has not been implicated in cases of idiosyncratic, acute liver injury with jaundice.

Likelihood score: C[HD] (probable cause of clinically apparent liver injury when given in high doses).

Mechanism of Injury

The mechanism by which interleukin-2 infusions might cause liver injury is unclear as it is a recombinant human protein and thus is unlikely to have direct hepatotoxicity. The induction of activated T cells, however, may be associated with some degree of hepatic inflammation and injury, but is not likely to cause frank acute liver damage. Furthermore, interleukin-2 also has multiple other actions that may account for its many side effects on endothelial cells, brain, kidney and hepatic function. Interleukin-2 has also been implicated in causing autoimmune conditions and vasculitis in other organs which may result in secondary effects on the liver.

Outcome and Management

The serum enzyme and bilirubin elevations during aldesleukin therapy are generally self-limited and benign. In situations in which ALT or AST levels rise and remain above 5 times ULN, dose modification or temporary discontinuation of the intravenous infusions is prudent.

Other recombinant cytokines and polypeptides used medically include interferon alfa, interferon beta and interferon gamma as well as several hematopoietic growth factors such as erythropoietin, granulocyte-macrophage colony stimulating factor and interleukin-11 (oprelvekin).

Drug Class: Antineoplastic Agents, Cytokines, Biologic Response Modifiers

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Aldesleukin – Proleukin®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Aldesleukin	110942-02-4	Cytokine	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 05 May 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of recombinant interleukin-2).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents does not discuss IL-2 or aldesleukin).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, Longo DL, Mitsiades C, Richardson P. 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. 1731-54.

(Textbook of pharmacology and therapeutics).

Fisher B, Keenan AM, Garra BS, Steinberg SM, White DE, DiBisceglie AM, Hoofnagle JH, et al. Interleukin-2 induces profound reversible cholestasis: a detailed analysis in treated cancer patients. J Clin Oncol 1989; 7: 1852-62. PubMed PMID: 2585024.

(Among 8 prospectively followed patients with malignancies receiving IL-2 [100,000 IU/kg 3 times daily for 5 days], serum bilirubin levels rose from 0.5 to 4.7 mg/dL [3.4 mg direct], becoming abnormal by day 3 and peaking on days 6-8 with a similar pattern of cholylglycine levels and mild rises in ALT, AST and Alk P becoming abnormal by day 6, all values returning to normal within one month).

Interleukin-2. Med Lett Drugs Ther 1990; 32 (826): 85-6. PubMed PMID: 2202892.

(Concise summary of the mechanism of action, clinical efficacy and safety of recombinant IL-2 before its approval, but in response to its availability on an experimental basis for use in renal cell cancer and malignant melanoma mentions side effects of increased capillary permeability with fluid retention, hypotension, renal insufficiency and pulmonary edema as well as severe malaise, fever, nausea, diarrhea, anemia and hyperbilirubinemia).

Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995; 13: 688-96. PubMed PMID: 7884429.

(Among 255 patients with metastatic renal cell cancer treated with aldesleukin in 7 clinical trials, the overall response rate was 14% and side effects were common [4% died], but most were rapidly reversible including capillary leak syndrome and hypotension; elevations in ALT occurred in 72%, alkaline phosphatase in 72%, and bilirubin in 85%; 11% of patients had "grade 4" increases in bilirubin and ALT, but all resolved with stopping IL-2 infusions without chronicity or mortality).

Noble S, Goa KL. Aldesleukin (recombinant interleukin-2). BioDrugs 1997; 7: 394-422. PubMed PMID: 18031103.

(Review of the mechanism of action, pharmacology, efficacy and safety of IL-2 as therapy of malignant melanoma mentions hepatic side effects of increase serum enzymes and bilirubin, intrahepatic cholestasis and jaundice).

Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, Ravaud A, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med 1998; 338: 1272-8. PubMed PMID: 9562581.

(Among 425 patients with metastatic renal cell cancer treated with IL-2 or interferon alfa or both, response rates as well as adverse events rates were higher with the combination; ALT or AST elevations above 5 times ULN occurring in 11% with IL-2 alone, 3% with interferon and 11% with the combination, but "all patients recovered and returned to their pretreatment status").

Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999; 17: 2105-16. PubMed PMID: 10561265.

(Among 270 patients with metastatic melanoma treated with high dose intravenous IL-2 [every 8 hours for 5 days repeated as tolerated], the response rate was 16% and acute toxicity was common with elevations of ALT in 39% [above 5 times ULN in 7%], bilirubin in 51% and Alk P in 13%).

Schlegel PJ, Samlowski WE, Ward JH. Autoimmune hemolytic anemia in a patient with chronic lymphocytic leukemia and renal cell carcinoma after treatment with high-dose intravenous bolus interleukin-2. J Immunother 2000; 23: 507-8. PubMed PMID: 10916762.

(66 year old man with renal cell cancer and CLL developed Coombs positive hemolytic anemia after a 5 day course of intravenous IL-2 which resolved with prednisone therapy).

Chi KH, Myers JN, Chow KC, Chan WK, Tsang YW, Chao Y, Yen SH, Lotze MT. Phase II trial of systemic recombinant interleukin-2 in the treatment of refractory nasopharyngeal carcinoma. Oncology 2001; 60: 110-5. PubMed PMID: 11244324.

(Among 14 patients with nasopharyngeal cancer who received 1 to 4 cycles of IL-2, no objective responses were seen and side effects were frequent including ALT or AST elevations in all 14 patients).

Abraham D, McGrath KG. Hypersensitivity to aldesleukin (interleukin-2 and proleukin) presenting as facial angioedema and erythema. Allergy Asthma Proc 2003; 24: 291-4. PubMed PMID: 12974198.

(61 year old woman developed facial erythema and swelling within a day of starting IL-2 which persisted during the 5 days of therapy, resolved after stopping and recurred with further courses; accompanied by specific anti-aldesleukin IgE; liver tests were reported to be normal).

Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, Seipp CA, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol 2003; 21: 3127-32. PubMed PMID: 12915604.

(Among 306 patients with metastatic renal cell cancer treated with high or low doses of IL-2 [72,000 or 720,000 IU/kg], responses were similar in frequency but more sustained with high doses that also had higher levels of toxicity; ALT or AST elevations above 5 times ULN occurring in 0.7% vs 3.2%).

Hauschild A, Weichenthal M, Balda BR, Becker JC, Wolff HH, Tilgen W, Schulte KW, et al. Prospective randomized trial of interferon alfa-2b and interleukin-2 as adjuvant treatment for resected intermediate- and high-risk primary melanoma without clinically detectable node metastasis. J Clin Oncol 2003; 21: 2883-8. PubMed PMID: 12885805.

(Among 255 patients with malignant melanoma given cycles of low dose interferon alfa and IL-2 or no treatment for 48 weeks, the combination therapy failed to show any effect, and while adverse events were common, they were generally self-limited; 9 patients required early discontinuation, one because of liver test abnormalities but details not given).

McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, Kirkwood JM, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol 2005; 23: 133-41. PubMed PMID: 15625368.

(Among 192 patients with metastatic renal cell carcinoma treated with high or standard doses of IL-2 and interferon, response rates were higher with higher doses [23% vs 10%] as were "hepatic toxicities" [12% vs 2%], and one patient on high doses died of capillary leak syndrome one week later).

Banerji A, Weller PF, Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's Syndrome). Immunol Allergy Clin North Am 2006; 26: 769-81. PubMed PMID: 17085290.

(Review of angioedema syndromes occurring with cytokine therapies including summary of a case report [Abraham 2003]).

Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, Sherry RM, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. Cancer 2008; 113: 293-301. PubMed PMID: 18457330.

(Review of 20 years of experience with treating 259 patients with metastatic renal cell cancer at the Surgery Branch, NIH mentions that responses occurred in 53 patients [20%] and AST elevations in 74 [29%] but were above 5 times ULN in only 5 [2%], while elevated bilirubin levels occurred in 155 [60%] but were "readily reversible" with stopping).

McDermott DF. The application of high-dose interleukin-2 for metastatic renal cell carcinoma. Med Oncol 2009; 26 Suppl 1: 13-7. PubMed PMID: 19148594.

(Review of the use of high dose IL-2 for metastatic renal cell cancer 17 years after its approval mentions objective response rates of 15% and complete responses of 7% that can result in long term survival; no discussion of toxicity).

INSIGHT-ESPRIT Study Group; SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. N Engl J Med 2009; 361: 1548-59. PubMed PMID: 19828532.

(Among 5806 patients with HIV infection on antiretroviral therapy in two controlled trials, the addition of IL-2 had no effect on rates of opportunistic infections or death; no discussion of acute toxicities).

Schwartzentruber DJ, Lawson DH, Richards JM, Conry RM, Miller DM, Treisman J, Gailani F, et al. gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med 2011; 364: 2119-27. PubMed PMID: 21631324.

(Among 185 patients with advanced melanoma treated with IL-2 with or without an experimental melanoma peptide vaccine, response rates were higher in the vaccine group [16% vs 6%] while toxicities were mostly similar, "hepatic" toxic effects occurring in 39% vs 40%).

Markowitz N, Lopardo G, Wentworth D, Gey D, Babiker A, Fox L, Tavel J; STALWART Study Group. Long-term effects of intermittent IL-2 in HIV infection: extended follow-up of the INSIGHT STALWART Study. PLoS One 2012; 7: e47506. PubMed PMID: 23082173.

(Long term follow up of HIV infected patients who were treated with IL-2 reported that the acute adverse events did not persist upon aldesleukin discontinuation).

Baldo BA. Side effects of cytokines approved for therapy. Drug Saf 2014; 37: 921-43. PubMed PMID: 5270293.

(Review of the safety and tolerance of therapeutic cytokines including aldesleukin [recombinant IL2]; mentions many of its severe side effects including cardiovascular, hemodynamic, pulmonary, gastrointestinal, endocrine, renal, infectious and dermatologic, but not liver toxicity or elevations in bilirubin or ALT levels).

McDermott DF, Cheng SC, Signoretti S, Margolin KA, Clark JI, Sosman JA, Dutcher JP, et al. The high-dose aldesleukin "select" trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res 2015; 21: 561-8. PubMed PMID: 25424850.

(Among 128 patients with metastatic renal cell cancer treated with IL-2, previously suggested predictive biomarkers for favorable outcome did not help with selection criteria for treatment; no discussion of adverse events).

Clark JI, Wong MKK, Kaufman HL, Daniels GA, Morse MA, McDermott DF, Agarwala SS, et al. Impact of sequencing targeted therapies with high-dose interleukin-2 immunotherapy. Clin Genitourin Cancer 2017; 15: 31-41. PubMed PMID: 27916626.

(Review of a large observational study of metastatic renal cell carcinoma including 352 patients who received high dose aldesleukin therapy mentions 5 treatment related deaths, but none were due to liver disease).