Brand Name: Unituxin

Generic Name: dinutuximab

Manufacturer[5]: United Therapeutics Corporation

Drug Class[1,4]: Antineoplastic Agent, Monoclonal Antibody

Uses:

Labeled Uses[1,2,3,4,5]: high risk neuroblastoma in pediatric patients achieving at least a partial response to prior first-line multiagent, multimodality therapy in combination with isotretinoin, sargramostim, and aldesleukin

Unlabeled Uses: None

Mechanism of Action[1,2,3,4,5]: Dinutuximab binds to glycolipid disialoganglioside 2 (GD2) located on the cell surface of neuroblastoma cells and induces cell lysis through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.

Pharmacokinetics[1,2,3,4,5]:

T_{max}	Not reported
V_d	5.4L
$t_{1/2}$	10 days
Clearance	0.21L/day
Protein Binding	Not reported
Bioavailability	100%

Metabolism: Not reported

Elimination: Not reported

Efficacy[6,7,8]:

Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34.

Study Design: open-label, multinational phase III study

Description of Study: *Methods:* Two-hundred-twenty-six patients with high-risk neuroblastoma were randomized to either receive standard therapy or immunotherapy. Patients eligible for enrollment but not randomization due to biopsy-proven residual disease after autologous stem-cell transplantation were nonrandomly assigned to receive immunotherapy. Standard therapy consisted of six 28-day cycles of isotretinoin. Immunotherapy consisted of six cycles of isotretinoin and five concomitant cycles of

dinutuximab in combination with alternating GM-CSF and interleukin-2. Dinutuximab was given to patients at a dose of 25mg/m^2/day for four consecutive days during five consecutive four-week cycles. GM-CSF was given daily for 14 days, starting 3 days before dinutuximab during cycles one, three, and five. During cycles two and four, patients were also given interleukin-2 for four days during week one at a dose of 3.0×106 IU/m^2/day. Interleukin-2 4.5×106 IU/m^2/day was also given for four days concurrently with dinutuximab during week two. The event-free survival between the two treatment groups was analyzed. *Outcome Results:* The two-year estimate for event-free survival was 66 ±5% for the immunotherapy group and 46±5% for the standard-therapy group (P=0.01). Estimated rate of overall survival was 86±4% for the immunotherapy group and 75±5% for the standard therapy group (P=0.02). Therefore, immunotherapy was shown to be superior to standard therapy in both event-free survival and overall survival rate. Analysis was also completed for a subgroup of patients who were 1 year of age or older and had stage 4 disease. Immunotherapy (63±6%) was greater than standard therapy (42±6%) for rate of event-free survival (P=0.02).

Limitations: The study failed to enroll enough patients to reach 80% power. The definition for event free survival and overall survival both included time to enrollment to death or to last contact with the patient. The similarities between the definitions make it hard to distinguish. The difference between the two treatment groups was not solely dinutuximab; therefore, it is difficult to conclude dinutuximab is entirely the reason for the beneficial results.

Conclusions: The study showed dinutuximab in conjunction with GM-CSF, interleukin-2, and isotretinoin significantly increased event free survival and overall survival among high-risk neuroblastoma patients. The overall survival was increased by approximately 9% while the event free survival was increased by approximately 20%. Further research is needed to identify the maximum effective dose that is also the least toxic dose.

Ozkaynak MF, Sondel PM, Krailo MD, Gan J, Javorsky B, Reisfeld RA, Matthay KK, Reaman GH, Seeger RC. Phase I study of chimeric human/murine anti-ganglioside G(D2) monoclonal antibody (ch14.18) with granulocyte-macrophage colony-stimulating factor in children with neuroblastoma immediately after hematopoietic stem-cell transplantation: a Children's Cancer Group Study. J Clin Oncol. 2000;18(24):4077-85.

Study Design: prospective cohort

Discussion: *Methods:* Twenty-two patients with neuroblastoma were enrolled in the study to receive escalating doses of dinutuximab with GM-CSF after hematopoietic stem-cell transplantation (HSCT). Patients started GM-CSF at least 72 hours before dinutuximab treatment. GM-CSF 250 mcg/m^2/day was administered as an IV infusion over two hours every day dinutuximab was given and for three days afterward. Dinutuximab was given as a five-hour IV infusion for four consecutive days. Initially, patients were administered

dinutuximab 20mg/m^2/day. Subsequent 28- day cycles increased the dose of dinutuximab by 10 mg/m^2/day. The maximum dose of dinutuximab evaluated was 50mg/m^2/day. The primary objective of the study was to define the maximum tolerated dose of the combination of dinutuximab and GM-CSF. *Outcome Results:* The maximum tolerated dose was 40mg/m^2/day. Neuropathic pain localized to the abdomen and lower extremities was experienced by 13 of the 19 patients. Two of those 13 patients had severe pain. No clear relationship was found between increased pain and dose escalation. Disease progression was reported in 10 of the 19 patients with a median follow-up of 40 months (range, 25-50 months). Progression occurred in the primary site in two patients, distant sites in seven patients, and in the primary and distant sites in one patient.

Limitations: One major weakness of this study is the sample size of only twenty-two patients. Not all patients started GM-CSF therapy on day zero; therefore, the duration of therapy varied between patients.

Conclusions: In this study, GM-CSF was given in addition to escalating doses of dinutuximab to discover the maximum-tolerated dose. The most frequently reported adverse event was neuropathic pain in the abdomen and lower extremities. At doses of 40mg/m^2/day of dinutuximab and below, adverse events of neuropathic pain, hypotension, capillary leak syndrome, etc. were manageable. Three patients treated with 50mg/m^2/day of dinutuximab experienced dose limiting toxicities including pain, nausea and vomiting, and urticarial eruption. Progression-free survival was not an end point of the study; however, it was analyzed. Only 10 out of 19 patients had disease progression which illustrates the treatments efficacy.

Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, Berthold F. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer. 2011 Jan 18;11:21.

Study Design: retrospective nonrandomized design

Discussion: *Methods:* Three hundred and thirty-four patients who participated in Cooperative German Neuroblastoma Trials NB90 and NB97 were included in the present study to analyze the long-term outcome of dinutuximab consolidation treatment. The dinutuximab treatment regimen consisted of a 20mg/m^2/day infusion over 8-12 hours for five concurrent days. The regimen was repeated every two months for a total of six cycles. The survival data of dinutuximab treated group was compared with the group receiving oral maintenance chemotherapy in the NB90 trial as well as with the patients who received no further consolidation treatment after initial therapy. The median observation time of this study was 11.11 years (range, 2.27-18.57 years). One hundred and sixty-four patients received dinutuximab. *Outcome Results:* There was no difference detected between dinutuximab treatment and oral maintenance chemotherapy in regards to event rate. The five-year event free survival rate was found to be 39.5 ± 2.7% and the five-year overall survival rate was 48.4 ± 2.7%. Dinutuximab consolidation resulted in a lower event rate compared to no consolidation (p=0.038). Overall survival rate for the dinutuximab group

was superior to the no consolidation therapy group (p=0.015) and to the oral maintenance chemotherapy group (p=0.023).

Limitations: The patient characteristics of the three treatment groups analyzed were not comparable in many areas. The number of patients in the dinutuximab group was more than double the amount of patients in the no consolidation group. Even though the median age at diagnosis was comparable, the range of ages at diagnosis were not. None of the patients in the oral maintenance chemotherapy group received a stem cell transplant compared to 62% of dinutuximab treated patients and 61% of patients who did not receive consolidation therapy. Values for some results were not reported; only p-values were reported. Therefore, clinicians are unable to determine clinical significance.

Conclusion: This follow-up study demonstrated the effectiveness of dinutuximab on event free survival and overall survival five years after treatment; however the results could not be compared to the other treatment groups due to the limitations previously stated. Future trials should look at long term outcomes in patients receiving maintenance therapy with dinutuximab, cytokines, and retinoic acid.

Contraindications[1,2,3,4,5]: History of anaphylaxis to dinutuximab

Precautions[1,2,3,4,5]:

Serious Infusion Reactions: Reactions including dyspnea, facial and upper airway edema, bronchospasm, stridor, urticarial, and hypotension generally occur during or within 24 hours of completing a dinutuximab infusion. Intravenous hydration and premedication with antihistamines, analgesics, and antipyretics is required prior to each dinutuximab infusion. Monitor patients for signs and symptoms of an infusion reaction during and for at least four hours after completion of each dinutuximab infusion.

Pain and Peripheral Neuropathy: Most patients experience pain commonly reported as abdominal pain, generalized pain, extremity pain, back pain, neuralgia, musculoskeletal chest pain, and arthralgia. Patients should be premedicated with analgesics, even intravenous opioids, prior to each dinutuximab infusion. The analgesics should be continued until two hours following the infusion. Severe peripheral sensory and motor neuropathy have been reported. Dinutuximab should be permanently discontinued in the event severe sensory neuropathy or moderate to severe peripheral motor neuropathy occurs.

Capillary Leak Syndrome: Approximately 25% of patients receiving dinutuximab experienced capillary leak syndrome. If capillary leak syndrome occurs, dinutuximab infusion should be immediately interrupted. Infusion reduction and/or discontinuation of therapy might also be necessary.

Hypotension: Closely monitored blood pressure and required intravenous hydration should be completed prior to each dinutuximab infusion. Appropriate medical management should be initiated in patients with a systolic blood pressure less than the lower limit of normal for the patient's age, or systolic blood pressure that decreased more than 15% from baseline.

Infection: Patients receiving dinutuximab should be warned about and monitored for signs and symptoms of systemic infection. Intravenous antibiotics or interruption of therapy may be required.

Neurological Disorders of the Eye: Neurological ocular toxicity experienced in clinical trials included blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, and papilledema. For visual disturbances not causing visual loss, interrupt dinutuximab treatment and upon resolution reinitiate with 50% of the original dinutuximab. Dinutuximab should be permanently discontinued in patients with recurrent signs or symptoms and in patients who experience loss of vision.

Bone Marrow Suppression: Patients' peripheral blood counts should be closely monitored due to the risk of anemia, thrombocytopenia, neutropenia, and febrile neutropenia.

Electrolyte Abnormalities: Serum electrolytes should be monitored daily for signs of hyponatremia, hypokalemia, and hypocalcemia.

Atypical Hemolytic Uremic Syndrome: A small number of patients receiving dinutuximab experienced hemolytic uremic syndrome resulting in renal insufficiency, electrolyte abnormalities, anemia, and hypertension. Dinutuximab should be permanently discontinued in patients that develop hemolytic uremic syndrome.

Embryo-Fetal Toxicity: Pregnant woman should be warned dinutuximab may cause fetal harm. Effective contraception should be used during dinutuximab treatment and for two months following treatment.

Adverse effects[1,2,3,4,5]:

Occurring in >10% of patients

Cardiovascular: Hypotension (60%), Capillary Leak Syndrome (40%), Tachycardia (19%), Edema (17%), Hypertension (14%)

Central Nervous System: Pain (85%), Peripheral Neuropathy (13%)

Dermatologic: Urticaria (37%)

Endocrine and Metabolic: Hyponatremia (58%), Hypokalemia (43%), Hypoalbuminemia (33%), Hypocalcemia (27%), Hypophosphatemia (20%), Hyperglycemia (18%), Hypertriglyceridemia (16%), Hypomagnesemia (12%)

Gastrointestinal: Increased serum alanine aminotransferase (56%), Vomiting (46%), Diarrhea (43%), Increased serum aspartate aminotransferase (28%), Decreased appetite (15%)

Genitourinary: Proteinuria (16%)

Hematologic and Oncologic: Thrombocytopenia (66%), Lymphocytopenia (62%), Anemia (51%), Neutropenia (39%), Hemorrhage (17%), Febrile neutropenia

Infection: Sepsis (18%), Infection (16%), Bacteremia (13%)

Renal: Increased serum creatinine (15%)

Respiratory: Hypoxia (24%)

Miscellaneous: Fever (72%). Infusion related reaction (60%)

Occurring in 1% to 10% of patients:

Central nervous system: Peripheral sensory neuropathy (9%), Peripheral motor neuropathy (1%)

Endocrine and Metabolic: Weight gain (10%), Electrolyte disturbance

Gastrointestinal: Nausea (10%)

Hematologic and Oncologic: Hemolytic-uremic syndrome (2%)

Hypersensitivity: Severe infusion related reaction

Ophthalmic: Blurred vision (2%), Blepharoptosis, Optic nerve damage, Papilledema, Photophobia

Renal: Renal insufficiency

Drug Interactions[1,2,3,4,5]:

The hypotensive effect may be enhanced by the following:

Alfuzosin, Amifostine, Second Generation Antipsychotic Agents, Barbiturates, Blood Pressure Lowering Agents, Brimonidine (Topical), Diazoxide, Duloxetine, Herbs with Hypotensive Properties, Hypotension-Associated Agents, Levodopa, Molsidomine, Naftopidil, Nicergoline, Nicorandil, Obinutuzumab, Pentoxifylline, Phosphodiesterase-5-Inhibitors, Prostacyclin Analogues, Quinagolide

Immunosuppressants may diminish the therapeutic effect of the following:

BCG (Intravesical), Echinacea, Nivolumab, Sipuleucel-T, Inactivated Vaccines

Immunosuppressants may enhance the immunosuppressive effect of the following:

Fingolimod, Roflumilast, Tofacitinib

Adverse effects of the following may be enhanced:

Belimumab, Clozapine, Deferiprone, Denosumab, Dipyrone, Leflunomide, Natalizumab, Pimercrolimus, Tacrolimus, Trastuzumab, Live Vaccines

Other Interactions:

Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test.

Dosing/Administration[1,2,3,4,5]:

Pediatric Dosing:

IV infusion of 17.5mg/m^2/day for four consecutive days for a maximum of five cycles in combination with GM-CSF, IL-2, and isotretinoin. Initiate infusion at 0.875mg/m^2/hr for 30 minutes and gradually increase to a maximum of 1.75mg/m^2/hr as tolerated.

During Cycles 1, 3, and 5 (24 day cycles each) infuse over 10-20 hours on days 4,5,6, and 7.

During Cycles 2 and 4 (32 day cycles each) infuse over 10-20 hours on days 8,9,10, and 11

Premedication

Analgesics: Administer 50mcg/kg morphine drip at 20-50 mcg/kg/hour immediately before dinutuximab infusion, during, and for two hours after infusion completion. Additional intravenous morphine of 25-50mcg/kg may be given once every two hours if needed. For patients unable to tolerate morphine, select fentanyl or hydromorphone.

Antihistamines: Twenty minutes prior to the dinutuximab infusion, administer diphenhydramine 0.5-1mg/kg/dose with a maximum of 50mg intravenously over 10-15 minutes. Readminister during the dinutuximab infusion every four to six hours as tolerated.

Antipyretics: Twenty minutes prior to the dinutuximab infusion, administer acetaminophen 10-15mg/kg/dose with a maximum of 650mg. Readminister during the dinutuximab infusion every four to six hours as needed for fever and pain. 5-10mg/kg/dose of ibuprofen may also be administered every six hours as needed for persistent fever and pain.

IV hydration: Just prior to initiating a dinutuximab infusion, administer 10mL/kg of 0.9% sodium chloride to infuse over one hour.

Renal Impairment: Not yet studied

Hepatic Impairment: Not yet studied

Use in special circumstances[1,2,3,4]:

Pregnancy: Dinutuximab is a monoclonal antibody and therefore may cause fetal harm by crossing the placenta mainly in the third trimester. Effective contraception should be utilized during therapy and for two months following therapy. Reproduction studies specifically for dinutuximab have not yet been completed.

Lactation: Not recommended as potentially serious adverse effects in breast-feeding infants cannot be ruled out.

Conclusion:

Dinutuximab was approved by the FDA as an orphan drug for high-risk neuroblastoma patients who had at least a partial response to prior first line multiagent, multimodality therapy. Dinutuximab works by binding to the glycolipid antigen disialoganglioside which is highly expressed on neuroblastoma cells' surfaces. Dinutuximab-containing regimens did not reach statistically significant event free survival; however, it was associated with significant five year overall survival rates. Serious but manageable adverse effects accompany dinutuximab therapy including severe pain, peripheral neuropathies, fever, hypotension, nausea, and vomiting. Premedication of analgesics, antiemetics, antihistamines, antipyretics, and IV hydration are necessary for patients to benefit from dinutuximab without experiencing the severe adverse effects. The approval of dinutuximab gives this pediatric population facing poor prognosis another therapeutic option in the fight for a cure.

Any other pertinent information about each drug should be included where appropriate:

Recommended References:

1. Dinutuximab. Lexi-Comp [Internet database]. Wolters Kluwer Clinical Drug Information, Inc. 2016. Available at: http://online.lexi.com.soleproxy.hsc.wvu.edu. Accessed August 13, 2016.
2. Dinutuximab. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2016. Available at: http://www.clinicalpharmacology.com. Accessed: August 13, 2016.
3. Dinutuximab. Facts & Comparisons 4.0 Online [Internet database]. Clinical Drug Information, Inc. 2016. Available at: http://online.factsandcomparisons.com. Accessed August 14, 2016.
4. Dinutuximab. Micromedex [Internet database]. Truven Health Analytics Inc., 2016. Available at http://www.micromedexsolutions.com. Accessed: August 14, 2016.
5. Unituxin (dinutuximab) [product monograph]. Silver Springs, MD: United Therapeutics Corporation; March 2015.
6. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34.
7. Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Niethammer D, Berthold F. Consolidation treatment with chimeric anti-GD2-antibody ch14.18 in children older than 1 year with metastatic neuroblastoma. J Clin Oncol. 2004 Sep1;22(17):3549-57.
8. Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, Berthold F. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer. 2011 Jan 18;11:21.

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