Rituximab DP

Pharmacological group of the substance Rituximab

Immunosuppressants

Antitumor agents-monoclonal agents

Pharmacological action – antitumor

Contents and product form

Concentrate for preparation of solution for infusion	1 ml
rituximab	10 mg
Additional ingredients: sodium citrate dihydrate; polysorbate 80; sodium chloride; hydrochloric acid or sodium hydroxide; water for injection	

in vials 10 (100 mg) or 50 (500 mg) ml

Characteristics

It is a synthetic (genetically engineered) chimeric mouse/human monoclonal antibody with specificity to the CD20 antigen found on the surface of normal and malignant B-lymphocytes. The structure of rituximab is that of class G1 immunoglobulins (IgG1 kappa) and its molecule contains mouse variable light and heavy chain fragments and a human constant segment. Rituximab consists of 2 heavy chains of 451 amino acids and 2 light chains of 213 amino acids and has a molecular weight of approximately 145 kD. The affinity of rituximab to the CD20 antigen is approximately 8 nM. Chimeric anti-CD20 antibodies are produced by cultured mammalian cells (Chinese hamster cell culture) in which a chimeric gene, obtained by genetic engineering, has been inserted.

Pharmacology

Rituximab binds specifically to the transmembrane antigen CD20 (a hydrophobic protein with a molecular weight of 35 kD). This antigen localizes on the surface of pre-B-lymphocytes and mature B-lymphocytes but is absent on hematopoietic stem cells, pro-B cells, normal plasma cells, and healthy cells of other tissues. This antigen is expressed in more than 90% of B-cell non-Hodgkin's lymphomas. CD20 antigen regulates all stages of B-lymphocyte maturation from the early stages and also functions as a regulator of calcium ion transport across the cell membrane. Once bound to the antibody, the CD20 molecule is not shed from the cell surface into the extracellular space and is not internalized, CD20 does not circulate in plasma as a free antigen.

Mechanism of antineoplastic action: The Fab fragment of rituximab binds to the CD20 antigen on lymphocytes and, with the participation of the Fc-domain, initiates immunological responses mediating B-cell lysis (shown in vitro). Possible mechanisms of cell lysis include complement-

dependent cytotoxicity (CDCT) and antibody-dependent cell-mediated cytotoxicity (ADCT). Rituximab has also been shown to induce apoptosis in human B-cell lymphoma DHL-4 cells.

Rituximab binds to lymphoid cells of the thymus, the white pulp of the spleen and most B-lymphocytes of peripheral blood and lymph nodes.

The median number of B-cells in peripheral blood after the first injection of rituximab decreases to below normal, and begins to recover after 6-9 months, returning to normal by 12 months after completion of therapy.

Pharmacokinetics

In patients who received single doses of rituximab 10, 50, 100, 250, or 500 mg/m2 by IV infusion, serum levels and T1/2 of rituximab increased in proportion to the dose. In 14 patients receiving therapy for 4 weeks at an intravenous infusion dose of 375 mg/m2, the mean serum T1/2 was 76.3 h (range, 31.5-152.6 h) after the first infusion and 205.8 h (range, 83.9-407.0 h) after the fourth infusion. The wide range of half-lives may reflect the variability in tumor mass among patients and changes in the population of CD20-positive (normal and malignant) B-cells after repeated infusions. When rituximab was administered at a dose of 375 mg/m2 as an IV infusion at weekly intervals to 203 patients, the mean Cmax after the fourth administration was 486 µg/mL (range, 77.5-996.6 µg/mL). Serum levels of rituximab were negatively correlated with tumor burden. Median serum levels at equilibrium were higher in responders compared to nonresponders, but no differences were found in elimination rates (serum T1/2 measurement). Rituximab is capable of cumulation and is detectable in the body for 3-6 months after the end of treatment.

Application of the substance Rituximab

B-cell non-Hodgkin's lymphomas (relapsed or chemoresistant, low-grade malignancy or follicular) in adults.

Contraindications

Hypersensitivity to rituximab or mouse proteins.

Limitations to use

High tumor load (foci size more than 10 cm), tumor infiltration of lungs, pulmonary insufficiency in anamnesis, cardiovascular diseases (angina pectoris, arrhythmia), neutropenia (less than 1500 cells/µL), thrombocytopenia (less than 75000 cells/µL), childhood (safety and efficacy in children are not established).

Administration during pregnancy and lactation

It is possible to administer to pregnant women only if the benefits of therapy exceed the potential risk for fetus. No long-term animal studies have been conducted to determine potential carcinogenicity, mutagenicity, or effects on fertility, and no toxic effects of rituximab on the animal reproductive system have been studied. Whether rituximab can have a damaging effect on the fetus when administered to pregnant women and whether it affects fertility is unknown. Class IgG immunoglobulins are known to pass through the placental barrier, so rituximab may cause

depletion of the fetal B-cell pool. During and for 12 months after treatment with rituximab, women of childbearing age should use effective contraception.

It is not known whether rituximab is excreted with breast milk in women. However, given that IgG class immunoglobulins circulating in the mother's blood pass into the breast milk, rituximab should not be administered to nursing mothers.

Side effects of the substance rituximab

Fatal infusion reactions. There have been reports of fatalities within 24 hours of rituximab infusion. These fatalities have resulted from the development of a complex of infusion reactions, including hypoxia, pulmonary infiltration, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred during the first infusion (see "*Infusion Reactions*" and "**Precautions**").

Tumor Lysis Syndrome. Acute renal failure developed with rituximab treatment and requiring dialysis has been reported and is fatal (see "*Renal Complications*" and "**Precautions**").

Rituximab causes rapid lysis of benign and malignant CD20-positive cells. The appearance of symptoms characteristic of tumor lysis syndrome (acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia) is described within 12-24 hours after the first infusion of rituximab.

Renal complications. Administration of rituximab was sometimes accompanied by severe renal toxicity, including acute renal failure with the need for dialysis and in several cases resulted in death. The incidence of renal toxicity was higher in patients with a high number of circulating malignant lymphocytes and a high tumor burden (see Tumor Lysis Syndrome), as well as in patients who were simultaneously treated with cisplatin in clinical trials. The combination of cisplatin with rituximab is not recommended. If such a combination is used, extreme caution and close monitoring of patients is required to detect serum creatinine elevation or oliguria in a timely manner.

Severe reactions of mucous membranes and skin . Severe reactions, sometimes involving death, have been described in connection with treatment with rituximab (see "Precautions"). These reactions include paraneoplastic vesicles (a rare condition that occurs in patients with malignancies), Stevens-Johnson syndrome, lichenoid dermatitis, vesicular bullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions in the observed cases ranged from 1 to 13 weeks after rituximab administration. Patients with severe skin reactions should not receive rituximab infusions ever again (the safety of rituximab reintroduction was not evaluated in this group of patients).

Most serious adverse reactions caused by rituximab include: infusion reactions, tumor lysis syndrome, mucosal and skin reactions, hypersensitivity reactions, cardiac arrhythmias, angina, and renal failure. Infusion reactions and lymphopenia are the most common.

Rituximab Monotherapy.

Table 1 presents data on adverse effects seen in patients receiving rituximab as monotherapy (N=356) in nonrandomized, noncomparative studies. Most patients received rituximab at a dose of 375 mg/m2 once weekly for 4 weeks. Among these patients, 39 had large tumors (?10 cm in size)

and 60 patients who received more than 1 course of rituximab therapy. The most severe side effects were combined in the column as "Grade 3 and 4 severity" according to the National Cancer Institute Common Toxicity Criteria.

Side effect data from clinical trials cannot be used directly for comparison with other clinical trials (because different trials are conducted with different sets of conditions) or for predicting side effects in routine medical practice, because patient conditions and other factors may differ from those that prevailed in the clinical trials. However, information on side effects observed in clinical trials can provide insight into the relative contribution of the substance itself and other factors to the development of adverse effects with drugs in the population.

Side effects observed in clinical trials with rituximab therapy

Risk factors associated with increased incidence of adverse events. Administration of 8 doses of rituximab once a week resulted in an increased incidence of grade 3 and 4 adverse reactions of up to 70% (compared to 57% with 4 doses). The incidence of grade 3 and 4 adverse reactions was similar in patients retreated with rituximab compared to initial treatment (58% and 57%, respectively).

Patients with high tumor burden (single foci sizes ?10 cm in diameter) (N=39) had an increased incidence of the following clinically significant adverse reactions - abdominal pain, anemia, dyspnea, hypotension, neutropenia - compared to patients with foci sizes <10 cm (N=195).

Infusion reactions (see also Fatal Infusion Reactions and Precautions). Most patients experience a mild to moderate infusion symptom complex of fever and chills/shivering during the first infusion. Other frequently observed infusion symptoms include nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. As a rule, these reactions occur within 30-120 min after the start of the first infusion and disappear after slowing or interruption of the drug administration and supportive measures (including intravenous infusions of saline, diphenhydramine and paracetamol). In an analysis of the administration of rituximab to 356 patients who received 1 weekly infusion for 4 (N=319) or 8 (N=37) weeks, the rate of such reactions was greatest at the first infusion, at 77%, and decreased with each subsequent infusion, to 30% (4th infusion) and 14% (8th infusion).

Infectious complications . Rituximab resulted in depletion of the B-cell pool in 70-80% of patients and decreased serum immunoglobulin levels in a small number of patients; lymphopenia with a median duration of 14 days (range, 1 to 588 days). The frequency of infections was 31%: 19% were bacterial infections, 10% were viral, 1% were fungal, and 6% were of unknown etiology (these percentages should not be added up because more than one type of infection may be reported in a single patient). Serious cases (grade 3 and 4), including sepsis, were reported in 2% of patients.

Hematologic adverse events. In clinical trials, patients treated with rituximab developed cytopenia in 48% of cases, including lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and neutropenia was 13 days (range, 2 to 116 days). After treatment with rituximab, 1 case of transient aplastic anemia (aplasia of the erythrocytic germline only) and 2 cases of hemolytic anemia have been described.

In addition, there are limited post-marketing reports of prolonged pancytopenia, bone marrow hypoplasia and late neutropenia (defined as occurring 40 days after the last rituximab injection) in patients with hematologic malignancies.

Cardiovascular adverse events. Grade 3 and 4 cardiovascular reactions include hypotension. Rare, fatal cases of heart failure with the development of symptoms weeks after initiation of rituximab treatment have been described.

Infusion should be discontinued if severe, life-threatening arrhythmias develop. Patients who develop clinically significant arrhythmias should have cardiac monitoring during and after subsequent infusions of rituximab. Patients with previous cardiac abnormalities, including arrhythmias and angina pectoris, may exhibit these symptoms during rituximab therapy, so they should be monitored throughout the infusion and immediately after.

Pulmonary symptomatology. In clinical trials, pulmonary adverse events were observed in 135 patients (38%). The most common respiratory adverse effects included: increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical trials and post-marketing observations, there have been limited reports of bronchiolitis obliterans present up to 6 months after rituximab infusion and limited reports of pneumonitis (including interstitial pneumonitis) present up to 3 months after rituximab infusion (some of these lung complications were fatal). The safety of resuming or continuing rituximab administration in patients with pneumonitis or bronchiolitis obliterans is unknown.

Hepatitis B reactivation. Hepatitis B virus reactivation with the development of fulminant hepatitis, liver failure and death has been reported in several patients with hematologic malignancy who received rituximab therapy. Most patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after the start of rituximab injections and approximately 1 month after the last dose.

Patients at high risk of hepatitis B virus infection should be screened before starting rituximab treatment for the virus. Hepatitis B virus carriers should be carefully screened for signs of active infection and hepatitis symptoms during rituximab therapy and several months thereafter. If the patient develops viral hepatitis, rituximab and any concomitant chemotherapy should be withdrawn and appropriate treatment, including initial antiviral therapy, prescribed. There is insufficient data demonstrating the safety of resuming treatment with rituximab in patients who develop hepatitis due to hepatitis B virus reactivation.

Immune/ autoimmune adverse reactions. Reactions such as uveitis, optic neuritis in patients with systemic vasculitis, pleurisy in patients with lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash have been reported.

Less common side effects observed. In clinical trials, less than 5% and more than 1% of patients observed had the following side effects (causal relationship to rituximab administration has not been established) - agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertension, hypoesthesia, hypoglycemia, injection site pain, insomnia, tear production disorders, malaise, irritability, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight loss

Interaction

When other monoclonal antibodies are administered for diagnostic purposes to patients who have antibodies against mouse proteins or anti-chimeric antibodies, they may develop allergic or hypersensitivity reactions.

When administered with cyclophosphamide, doxorubicin, vincristine, prednisolone, no increase in the incidence of toxic effects has been noted. Medicines which inhibit bone marrow hematopoiesis increase the risk of myelosuppression.

Overdose

There were no observed cases of overdose in human clinical trials. However, single doses over 500 mg/m2 have not been studied.

Dosage and administration

The concentrate is pre-diluted in an infusion bottle (bag) with sterile, apyrogenic 0.9% aqueous sodium chloride solution or 5% aqueous glucose solution to a concentration of 1-4 mg/ml; administered by drip at a dose of 375 mg/m2 body surface once a week for 4 weeks; the initial infusion rate is 50 mg/h, with a gradual increase of 50 mg/h every 30 min (maximum rate 400 mg/h); subsequent treatments may start at 100 mg/h and increase by 100 mg/h every 30 min to the maximum rate (400 mg/h).

Precautions

Infusions are only possible in a hospital setting under the close supervision of an oncologist or hematologist experienced in such treatment, and everything necessary for full resuscitation measures must be on hand. Due to the risk of hypotension, withdrawal of antihypertensive drugs 12 hours before and during the entire infusion is recommended. Infusion regimens should be strictly followed; intravenous jet or bolus infusion is unacceptable.

To prevent the development of "cytokine release syndrome", premedication is required 30-60 min before each procedure: analgesic/antipyretic (e.g., paracetamol) and antihistamine (diphenhydramine, etc.), and corticosteroids if there is an increased risk of allergic reactions. Mild or moderate reactions can be eliminated by reducing the rate of administration, which can be increased again once the symptoms disappear. In most cases of patients with non-life-threatening adverse reactions, treatment with rituximab has been completed.

Tumor lysis syndrome. Individual cases of fatal outcomes were observed due to the development of this syndrome in patients receiving rituximab. The risk of developing the syndrome is higher in patients with a high number of circulating malignant lymphocytes (≥25000 cells/mm2) or with a high tumor burden. Patients at risk of tumor lysis syndrome should be given preventive measures (close observation, appropriate laboratory monitoring, including monitoring of renal function and electrolyte balance, if symptoms of rapid tumor lysis develop - appropriate drug therapy, correction of electrolyte disturbances, dialysis). In a limited number of cases after complete resolution of symptoms, rituximab therapy was continued in combination with prophylaxis of rapid tumor lysis syndrome.

Caution should be exercised (lower infusion rate, close monitoring) in patients with single tumor foci larger than 10 cm in diameter or with a circulating malignant cell count ≥25000 cells/mm3 due to an

increased incidence of severe adverse reactions. Because of the high risk of "cytokine release syndrome" in patients with anamnestic signs of pulmonary insufficiency and with tumor infiltration of the lungs, administration is possible under close supervision and only if other therapies are ineffective. If "cytokine release syndrome" develops, the infusion should be stopped immediately and intensive symptomatic therapy should be initiated.

Caution is prescribed for patients with neutropenia (less than 1500 cells per 1 μl) and thrombocytopenia (less than 75000 cells per 1 μl); regular control of peripheral blood cells composition is necessary during the course.

Immunization. The safety of immunization with any vaccine, especially live viral vaccines, after treatment with rituximab has not been evaluated. The ability to give a primary or anamnestic humoral response to any vaccine has also not been studied.

Effects on driving and operating machinery

It is not known whether rituximab affects driving and operating machinery, although the pharmacologic activity and adverse events described do not suggest such an effect.

Manufacturer

"Dong-Pha South Korea

Storage conditions

Store in a dark place at 2-8℃.

Keep out of the reach of children.

Shelf life

2.5 years.

Do not use after expiration date stated on the package.