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(54) **CCI-779 FOR TREATING MANTLE CELL LYMPHOMA**

CCI-779 ZUR BEHANDLUNG VON MANTELZELLLYMPHOM

CCI-779 POUR TRAITER DES LYMPHOMES A CELLULES DU MANTEAU

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(73) Proprietor: **MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH**
Rochester, MN 55905 (US)

(72) Inventors:
- **WITZIG, Thomas, E.**
  Rochester, MN 55902 (US)
- **KAUFMANN, Scott, H.**
  Rochester, MN 55901 (US)

(74) Representative: **Dörries, Hans Ulrich**
df-mp
Fünf Höfe
Theatinerstrasse 16
80333 München (DE)

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Description

BACKGROUND OF THE INVENTION

[0001] This invention relates to the use of rapamycin 42-ester with 3-hydroxy-2-(hydroacymethyl)-2-methyl-propionic acid (CCI-779) in the treatment or inhibition of mantle cell lymphoma.

[0002] Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is an ester of rapamycin. Rapamycin, also termed sirolimus, is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus.* The preparation and use of hydroxyesters of rapamycin, including CCI-779, are described in U.S. Patents 5,362,718 and 6,277,983.

[0003] CCI-779 has been described as having *in vitro* and *in vivo* activity against a number of tumor cell types. It is hypothesized that CCI-779 delays the time to progression of tumors or time to tumor recurrence. This mechanism of action is more typical of cytostatic rather than cytotoxic agents and is similar to that of sirolimus.

[0004] CCI-779 binds to and forms a complex with the cytoplasmic protein FKBP, which inhibits an enzyme, mTOR (mammalian target of rapamycin, also known as FKBP12-rapamycin associated protein [FRAP]). Inhibition of mTOR's kinase activity inhibits a variety of signal transduction pathways, including cytokine-stimulated cell proliferation, translation of mRNAs for several key proteins that regulate the G1 phase of the cell cycle, and IL-2-induced transcription, leading to inhibition of progression of the cell cycle from G1 to S.

[0005] Mantle cell lymphoma (MCL) a cancer of the B-lymphocytes housed in the mantle regions of the lymph nodes, is a unique subtype of non-Hodgkin's lymphoma (NHL) which is characterized by a specific chromosomal translocation of the bcl-1 gene (t(11;14)(q13,q32)) and subsequent over-production of the gene product cyclin D1. The proto-oncogene bel-1 (which stands for B-cell lymphoma/leukemia) is one offive genes on the section of chromosome 11 which are translocated in MCL, but it is the only one expressed in MCL. The unique nature of lymphocytes and, in particular, the site bcl-1 occupies on chromosome 14 account for at least some of the bizarre behavior of MCL cells.

[0006] MCL represents approximately 10% of all NHL. The median age of onset is approximately 60 years and there is a higher incidence in males [Decaudin, D., et al, Leuk Lymphoma 37: 181-4(2000)]. Patients typically present in advanced stage and extranodal sites are often involved. For example, some patients present with prominent lymphocytosis and may be mistaken for chronic lymphocytic leukemia. [Wong, K. F., et al., Cancer 86: 850-7 (1999)], Others present with multiple polyps in the colon that can produce gastrointestinal bleeding [Hashimoto, Y., et al, Hum Pathol 30:581-7 (1999)]. AnoateraamuaIpiMentationiB&atofBMasive splenomegaly and minimal lymphadenopathy [Molina, T. J., et al, Virchows Arch 437:591-8(2000)]. Patients with MCL have been demonstrated to have a significantly worse prognosis than those with other low-grade histologies with a median survival of 3-4 years [Weisenburger, D. D., et al., Am J Hematol 64:190-6 (2000); Hiddemann, W., et al., Journal of Clinical Oncology 16: 1922-30 (1998) ; Samaha, H., et al., Leukemia 12: 1281-7, (1998); Callea, V., et al., Haematologica 83 : 993-7(1998)].

[0007] The treatment of MCL has remained problematic despite the availability of purine nucleoside analogues, stern cell transplantation, and monoclonal antibody therapy with rituximab. Each of these modalities can produce tumor responses in MCL, but the disease typically recurs and requires additional therapy. There is no one treatment regimen that can be considered the treatment of choice for patients with new, untreated MCL. Most patients are treated with combinations of rituximab and chemotherapy-usually R-CHOP or a purine nucleoside analogue and rituximab. patients who are eligible for high-dose therapy with stern cell support are usually transplanted in first remission.

[0008] Less than 50% of MCL patients achieve a complete remission (CR) with current therapy and few patients achieve durable remissions. The typical scenario is that the patient will respond to chemotherapy, but the responses are usually partial and the time to progression short [Oinonen, R., et al., European Journal of Cancer 34: 329-36(1998)].

[0009] Huang and Houghton (Current Opinion In Investigational Drugs, 2002, voL 3, no. 2,295-304; ISSN: 0967-8298) describe rapamycin generally and its activity as an immunosuppressant and antitumor agent. Huang and Houghton teach rapamycin exerts antitumor properties against different B-cell lymphoma cell lines. Huang and Houghton describe CCI-779 is an analogue of rapamycin with some similar cellular effects as those of rapamycin. However, Huang and Houghton do not teach or suggest CCI-779 for treating or inhibiting mantle cell lymphoma, which is a unique subtype of non-Hodgkin's lymphoma.

[0010] Elit (Current Opinion in Investigational Drugs, 2002, voL 3, no. 8,1249-1253; ISSN: 1472-4472) teaches CCI-779 is an ester of rapamycin and has antitumor properties. Elit teaches CCI-779 is being studied in various clinical studies. Blit further teaches that CCI-779 has been shown to stabilize non-Hodkin's lymphoma. However, Elit does not teach or suggest CCI-779 for treating or inhibiting mantle cell lymphoma, which is a unique subtype of non-Hodgkin's lymphoma.

[0011] Alexandre and Armand (Cancer Bulletin, 1999, vol. 86, no. 10, 808-811; ISSN: 0008-5448) teach that rapamycin has immunosuppressant and antitumor properties. Alexandre and Armand further teach that CCI-779 is an analogue of rapamycin with the advantage of being administrable by a parenteral route, e.g., intravenous. Alexandre and Armand do not teach or suggest CCI-779 for treating or inhibiting mantle cell lymphoma, which is a unique subtype of non-Hodgkin's lymphoma.

[0012] Hidalgo and Rowinsky (Oncogene, 2000, vol.

19, no. 56, 6680-6686; ISSN: 0950-9232) teach that CCI-779 is an ester of rapamycin that inhibits the cell cycle, i.e., has antitumor properties. In particular, the article by Hidalgo and Rowinsky is directed to a study and conclusions evaluating the feasibility, pharmacokinetics, and biological effects of escalating doses of CCI-779. Hidalgo and Rowinsky do not teach or suggest CCI-779 for treating or inhibiting mantle cell lymphoma, which is a unique subtype of non-Hodgkin's lymphoma.

[0013] WO 03/020266 is drawn to antitumor combinations comprising CCI-779 and another antitumor agent, EKB-569. Generally, WO 03/020266 teaches that rapamycin is useful for treating, *inter alia* adult T-cell leukemia/lymphoma and that CCI-779 is an analogue of rapamycin. WO 03/020266 further teaches that CCI-779 has been shown to inhibit the growth of various tumour cells. However, WO 03/020266 does not teach or suggest CCI-779 for treating or inhibiting mantle cell lymphoma, which is a unique subtype of non-Hodgkin's lymphoma.

[0014] Mantle cell lymphoma remains a difficult disease to treat once it has relapsed and patients are typically treated with multiple regimens with a short time to progression between treatments.

SUMMARY OF THE INVENTION

[0015] The invention provides for the use of a CCI-779 in preparing a medicament for treating or inhibiting mantle cell lymphoma in a subject.

[0016] Also described is a pharmaceutical composition for treating or inhibiting mantle cell lymphoma which comprises a CCI-779 in unit dosage form in association with a pharmaceutically acceptable carrier.

[0017] Also described is a pharmaceutical pack containing a course of treatment of mantle cell lymphoma for one individual mammal, comprising a container having a CCI-779 in unit dosage form.

[0018] Also described is a method and kits useful in the treatment or inhibition of mantle cell lymphoma. Other aspects and advantages of the invention will be apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0019] As used in accordance with this invention, the term "treatment" means treating a mammal having mantle Cell lymphoma by providing said mammal with an effective amount of a CCI-779 with the purpose of inhibiting growth of the lymphoma in such mammal, eradication of the lymphoma, or palliation of the lymphoma.

[0020] As used in accordance with this invention, this term "inhibition" means inhibiting the onset or progression of mantle cell lymphoma in a mammal having or susceptible to developing such disease by providing said mammal an effective amount of CCI-779.

[0021] As used in accordance with this invention, the term "providing" means either directly administering CCI-779 or administering a pharmaceutical salt of CCI-779 which will form an effective amount of CCI-779 in the body. Throughout this specification and claims, the term "a CCI-779" encompasses CCI-779, an such pharmaceutical salts wich provide an effective amount of CCI-779 to the subject.

[0022] The preparation of CCI-779 is described in U.S. Patent 5,362,718 . A regiospecific synthesis of CCI-779 is described in US Patent 6,277,983. Still another regiospecific method for synthesis of CCI-779 is described in US Patent Application No. 10/903,062, filed July 30, 3004, and its counterpart. International Patent Application PCT/US2004/22860, filed July 15, 2004.

[0023] The ability of CCI-779 to treat or inhibit mantle cell lymphoma was evaluated in a clinical trial. Briefly, 18 patients (mean age 72 years, range 38-89 years) were treated with an intravenous dose of 250 mg CCI-779 on days 1, 8, 15, and 22 of a 4 week treatment cycle, for up to a maximum of 12 cycles. Of these patients, 15 were stage IV, 2 were stage III, and 1 was stage II. The overall response rate was 44.4% (95% CI; 24%-68%) and thus satisfied the criteria as early evidence of efficacy in this patient group. One patient had a complete response (CR), and 7 patients had a partial response (PR). Only 3 patients progressed before the end of the cycle. Based on the results obtained in this clinical trial, CCI-779 is useful in the treatment or inhibition of mantle cell lymphoma.

[0024] When CCI-779 is used in the treatment or inhibition of mantle cell lymphoma, it is projected that a subject will be provided with a weekly dosage of 10 to 250 mg of CCI-779 per week. Treatment typically consists of a monthly cycle composed of weekly dosage administrations, although weekly or bi-weekly cycles may be selected. A subject may undergo from one to twelve continuous monthly cycles. Alternatively, a subject may undergo one cycle, cease treatment, and then undergo another cycle.

[0025] Oral or intravenous infusion are the preferred routes of administration, with intravenous being more preferred. Initial intravenous dosages are typically projected to be tenfold less than the oral dosages. For example, intraveous dosages may be in the range of 10 mg/week to 175 mg/week, or from 20 mg/week to 150 mg/week, or more desirably, from 25 mg/week to 75 mg/week; whereas, oral doses maybe in the range of 100 mg/week to 250 mg/week, 125 mg/week to 225 mg/week, or 150 mg/week to 200 mg/week. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated.

[0026] Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Optionally, the dosage is then decreased for a week, biweek, or cycle, as desired or necessary.

[0027] Preferably, the pharmaceutical composition is

in unit dosage form, *e.g.* as tablets, capsules, or prefilled vials or syringes. In such form, the composition is subdivided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

[0028] Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins and gums etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed. Preferred oral formulations for rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid are disclosed in US Published Patent Application, US 2004-0077677 A1 (also USSN 10/663,506).

[0029] In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

[0030] The compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0031] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Preferred injectable formulations for rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid are disclosed in US 2004-0167152 (also USSN 10/626,943).

[0032] In this embodiment, the injectable formulation useful in the invention provides a CCI-779 cosolvent concentrate containing a parenterally acceptable solvent and an antioxidant as described above and a parenteral formulation containing a CCI-779, composed of CCI-779, a parenterally acceptable cosolvent, an antioxidant, a diluent solvent, and a surfactant. Any given formulation useful in this invention may contain multiple ingredients of each class of component. For example, a parenterally acceptable solvent can include a non-alcoholic solvent, an alcoholic solvent, or mixtures thereof. Examples of suitable non-alcoholic solvents include, *e.g.,* dimethylacetamide, dimethylsulfoxide or acetonitrile, or mixtures thereof. "An alcoholic solvent," may contain one or more alcohols as the alcoholic solvent component of the formulation. Examples of solvents useful in the formulations invention include ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or mixtures thereof. These cosolvents are particularly desirable because degradation via oxidation and lactone cleavage occurs to a lower extent for these cosolvents. Further, ethanol and propylene glycol can be combined to produce a less flammable product, but larger amounts of ethanol in the mixture generally result in better chemical stability. A concentration of 30 to 100%v/v of ethanol in the mixture is preferred.

[0033] In this embodiment, the stability of CCI-779 in parenterally acceptable alcoholic cosolvents is enhanced by addition of an antioxidant to the formulation. Acceptable antioxidants include citric acid, d,1-α-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof. Generally, the parenteral formulations useful in this embodiment of the invention will contain an antioxidant component(s) in a concentration ranging from 0.001% to 1% w/v, or 0.01% to 0.5% w/v, of the cosolvent concentrate, although lower or higher concentrations may be desired. Of the antioxidants, d,1-α-tocopherol is particularly desirable and is used at a concentration of 0.01 to 0.1% w/v with a preferred con-

centration of 0.075% w/v of the cosolvent concentrate.

[0034] In certain embodiments, the antioxidant component of the formulation of the invention also exhibits chelating activity. Examples of such chelating agents include, *e.g.,* citric acid, acetic acid, and ascorbic acid (which may function as both a classic antioxidant and a chelating agent in the present formulations). Other chelating agents include such materials as are capable of binding metal ions in solution, such as ethylene diamine tetra acetic acid (EDTA), its salts, or amino acids such as glycine are capable of enhancing the stability of CCI-779. In some embodiments, components with chelating activity are included in the formulations of the invention as the sole "antioxidant component". Typically, such metal-binding components, when acting as chelating agents are used in the lower end of the range of concentrations for the antioxidant component provided herein. In one example, citric acid enhanced the stability of CCI-779 when used at a concentration of less than 0.01% w/v. Higher concentrations are less stable solutions and thus, less desirable for products to be subject to long-term storage in liquid form. Additionally, such chelating agents may be used in combination with other antioxidants as part of the antioxidant component of the invention. For example, an acceptable formulation may contain both citric acid and d,1-α-tocopherol. Optimal concentrations for the selected antioxidant(s) can be readily determined by one of skill in the art, based upon the information provided herein.

[0035] Advantageously, in certain embodiments of the parenteral formulations useful in the invention, precipitation of CCI-779 upon dilution with aqueous infusion solutions or blood is prevented through the use of a surfactant contained in the diluent solution. The most important component of the diluent is a parenterally acceptable surfactant. One particularly desirable surfactant is polysorbate 20 or polysorbate 80. However, one of skill in the art may readily select other suitable surfactants from among salts of bile acids (taurocholate, glycocholate, cholate, deoxycholate, etc.) which are optionally combined with lecithin. Alternatively, ethoxylated vegetable oils, such as a pegylated castor oil [e.g., such as PEG-35 castor oil which is sold, *e.g.,* under the name Cremophor EL, BASF], vitamin E tocopherol propylene glycol succinate (Vitamin E TGPS), and polyoxyethylene-polyoxypropylene block copolymers can be used in the diluent as a surfactant, as well as other members of the polysorbate family such as polysorbate 20 or 60 Other components of the diluent may include water, ethanol, polyethylene glycol 300, polyethylene 400, polyethylene 600, polyethylene 1000, or blends containing one or more of these polyethylene glycols, propylene glycol and other parenterally acceptable cosolvents or agents to adjust solution osmolarity such as sodium chloride, lactose, mannitol or other parenterally acceptable sugars, polyols and electrolytes. It is expected that the surfactant will comprise 2 to 100% w/v of the diluent solution, 5 to 80% w/v, 10 to 75% w/v, 15 to 60 % w/v, and preferably, at least 5% w/v, or at least 10% w/v, of the diluent solution.

[0036] A parenteral formulation useful in the invention can be prepared as a single solution, or preferably can be prepared as a cosolvent concentrate containing CCI-779, an alcoholic solvent, and an antioxidant, which is subsequently combined with a diluent that contains a diluent solvent and suitable surfactant Prior to use, the cosolvent concentrate is mixed with a diluent comprising a diluent solvent, and a surfactant. When CCI-779 is prepared as a cosolvent concentrate according to this invention, the concentrate can contain concentrations of CCI-779 from 0.05 mg/mL, from 2.5 mg/mL, from 5 mg/mL, from 10 mg/mL or from 25 mg/mL up to 50 mg/ml. The concentrate can be mixed with the diluent up to approximately 1 part concentrate to 1 part diluent, to give parenteral formulations having concentrations of CCI-779 from 1mg/mL, from 5 mg/mL, from 10 mg/mL, from 20 mg/mL, up to 25 mg/ml. For example the concentration of CCI-779 in the parenteral formulation may be from 2.5 to 10 mg/mL. This invention also covers the use of formulations having lesser concentrations of CCI-779 in the cosolvent concentrate, and formulations in which one part of the concentrate is mixed with greater than 1 part of the diluent, *e.g.,* concentrate: diluent in a ratio of 1:1.5, 1:2, 1:3, 1:4 ,1:5, or 1:9 v/v and so on, to CCI-779 parenteral formulations having CCI-779 concentration down to the lowest levels of detection.

[0037] Typically the antioxidant may comprise from 0.0005 to 0.5% w/v of the formulation. The surfactant may for example comprise from 0.5% to 10% w/v of the formulation. The alcoholic solvent may for example comprise from 10% to 90% w/v of the formulation.

[0038] The parenteral formulations useful in this invention can be used to produce a dosage form that is suitable for administration by either direct injection or by addition to sterile infusion fluids for intravenous infusion.

[0039] For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[0040] Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream

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