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(54) **Egy HDAC inhibitort és egy szteroidot tartalmazó gyógyszerészeti készítmény és ennek alkalmazása**

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(54) **A PHARMACEUTICAL COMPOSITION COMPRISING A HDAC INHIBITOR AND A STEROID AND THE USE THEREOF.**

PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT EINEM HDAC-HEMMER SOWIE STEROID DARAUS UND VERWENDUNG DAVON

COMPOSITION PHARMACEUTIQUE COMPRENANT UN INHIBITEUR DES HDAC ET UN STÉROÏDE, ET SON UTILISATION

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Description

FIELD OF INVENTION

[0001] The invention relates to a histone deacetylase (HDAC) inhibitor and a steroid for use in the pretreatment of a disease selected from the group consisting of diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukaemia, T cell lymphoma and Hodgkin lymphoma, wherein the HDAC inhibitor is selected from the group consisting of valproic acid, valproate semisodium, sodium valproate, magnesium valproate or mixtures thereof, and wherein the steroid is selected from the group consisting of prednisone, prednisolone, dexamethasone or betamethasone.

BACKGROUND OF INVENTION

[0002] Cancer can be defined as an abnormal growth of cells which exhibit signs of uncontrolled proliferation and disturbed programmed cell death. From a classical view, sequential genetic events lead to malignant transformation, resulting in a cell clone that does not respect the integrity of other cells and tissues, and may eventually metastasize. Cancer can involve any tissue of the body and have many different forms in each body area.

[0003] Malignant lymphoma can be defined as a malignant transformation of the lymphatic cells of the hematopoietic system. Lymphomas can be divided into aggressive lymphomas and indolent lymphomas. Aggressive lymphomas are characterized by a rapid growth pattern, and can have dramatic clinical features. However, aggressive lymphomas can reach a complete cure by treatment with chemotherapy, radiotherapy and monoclonal antibodies. In contrast, indolent lymphomas (e.g., follicular lymphomas) have a slow growth pattern, and usually a more modest clinical presentation. However, although indolent lymphomas cannot reach a complete cure by standard lymphoma treatment, they can sometimes be cured by allogeneic stem cell transplantation. The median survival time for follicular lymphomas is 8-10 years. Diffuse large B cell lymphoma and Hodgkin lymphoma belong to the group of aggressive lymphomas, while follicular lymphoma and chronic lymphocytic leukaemia are indolent lymphomas. Myelomas consist of malignantly transformed plasmacells. They are related to indolent lymphomas, but are usually considered an entity of their own. The prognosis is pessimistic, with a median survival time of 5-7 years.

[0004] Diffuse Large B-cell Lymphoma (DLBCL) is the most frequent subtype of malignant lymphoma, with an incidence of about 500 cases/year in Sweden. DLBCLs constitute 60-70% of the group of aggressive lymphomas. The median age at diagnosis is 70 years, and DLBCL is slightly more common in males than in females. Standard first line treatment of DLBCL is chemotherapy consisting of a combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). During recent years addition of the CD20 antibody rituximab has become international clinical standard (R-CHOP), leading to improved progression-free, event-free, disease-free and overall survival (Morrison, Expert Rev Anticancer Ther, 2008; 8(10): pp. 1651-1658*).* Still, since as many as 45 % of patients die from their disease, there is a pronounced clinical need to increase progression-free survival in DLBCL patients.

[0005] Regulation of DNA transcription is complex and the mechanisms involved are only partially known. Histone Deacetylases (HDACs) can regulate expression of tumour suppressor genes and activities of transcription factors involved in both cancer initiation and progression. HDACs act through alteration of either DNA or the structural components of chromatin by histone deacetylation, thus affecting the three dimensional conformation of DNA without changing or interrupting its sequence (epigenetic modifications). It has also been suggested that they may alter the sensitivity to DNA damaging chemotherapy through modulation of chromatin structure. Along these lines, several in vitro studies have suggested that HDAC inhibitors can synergize with chemotherapy.

[0006] During recent years numerous HDAC inhibitors have been developed. They can be divided into four classes; hydroxamic acids/carbamic acids, cyclic peptides, aliphatic acids and benzamides. For example, vorinostat and romidepsin are approved for the treatment of cutaneous T-cell lymphoma lymphoma by the FDA (Food and drug administration), and are currently evaluated in the treatment of other malignancies.

[0007] The clinically most well-known inhibitor is the anticonvulsant valproic acid, which has been utilized in the treatment of epilepsy since the 1970s. Valproic acid belongs to the aliphatic acid class of inhibitors.

[0008] EP1 427 403 discloses the use of valproic acid (VPA) and pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of human cancer in combination with irradiation treatment wherein the human cancer is selected from the group consisting of breast cancer, colon cancer, head and neck cancer, small cell lung carcinoma and cancer of blood cells. According to EP1602371, VPA could also be used in combinatorial therapy with one or several other anti-cancer treatments which target mechanisms strikingly different from each other such as chemotherapeutic and cytotoxic reagents, differentiation-inducing reagents (e.g.retinoic acid, vitamin D, cytokines), hormonal therapy, immunological approaches and, more recently, the development of anti-angiogenic approaches and gene therapy.

[0009] US2008/0194690 discloses the use of an HDAC inhibitor, i.e., certain carbamic acid compounds, such as belinostat (PXD101) in combination with cyclodextrin, arginine or meglumine for the treatment of a number of diseases,

including cancer, wherein the solubility of the HDAC inhibitor is enhanced by the addition of one or more of cyclodextrin, arginine or meglumine.

[0010] Kitazoe K I et al.: "Walproic acid exerts anti tumor as well as antiangiogenic effects on myeloma", International journal of hematology, vol 89, no. 1, 18 december 2008, discloses the ability of VPA to induce cell death in several myeloma cell lines and to potentiate the anti-myeloma effects of dexamethasone.

[0011] Tran T et al.: "Enhancement of folate receptor alpha expression in tumor cells through the glucocorticoid receptor: a promising means to improved tumor detection and targeting", Cancer research, vol 65, no. 10, 15 May 2005, discloses the ability of the HDAC inhibitors Trichostatin A and VPA to potentiate dexamethasone induced expression of folate receptor alpha in FR positive tumours.

SUMMARY OF THE INVENTION

[0012] The invention relates to the unique finding that a combination of a HDAC inhibitor together with a steroid will improve the survival of a patient suffering from cancer such as lymphoma. The compounds are pharmaceutically acceptable compounds and are to be administrated at least prior to further treatments as a pretreatment. The substances are administrated together or separately and administrated as pharmaceutically acceptable compounds.

[0013] It has been found that the steroid could be utilized to increase the response from the patient upon treatment with the HDAC inhibitor as well as reduce the side-effects such as somnolence.

[0014] In a first aspect, the invention relates to a histone deacetylase (HDAC) inhibitor and a steroid for use in the pretreatment of a disease selected from the group consisting of diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukaemia, T cell lymphoma and Hodgkin lymphoma, wherein the HDAC inhibitor is selected from the group consisting of valproic acid, valproate semisodium, sodium valproate, magnesium valproate or mixtures thereof, and wherein the steroid is selected from the group consisting of prednisone, prednisolone, dexamethasone or betamethasone.

[0015] Thus, by providing such use the survival rate for a person suffering from cancer such as lymphoma is increased as well as it is for the first time possible to treat elder people, requiring a lower dose of chemotherapy, with maintained efficacy.

DETAILED DESCRIPTION OF THE INVENTION

HDAC and steroid

[0016] In a fist aspect the invention relates to to a histone deacetylase (HDAC) inhibitor and a steroid for use in the pretreatment of a disease selected from the group consisting of diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukaemia, T cell lymphoma and Hodgkin lymphoma, wherein the HDAC inhibitor is selected from the group consisting of valproic acid, valproate semisodium, sodium valproate, magnesium valproate or mixtures thereof, and wherein the steroid is selected from the group consisting of prednisone, prednisolone, dexamethasone or betamethasone. Further the HDAC inhibitor may be valproic acid, such as sodium valproate or magnesium valproate or mixtures thereof. Examples includes vorinostat (marketed under the trade mark Zolinza® in the US), romidepsin (marketed under the trade mark Istodax® in the US), panobinostat. One form of valproic acid is when it is mixed with sodium valproate, i.e., a mixture of the acid and salt (valproate semisodium) and marketed under the various brand names Depakote, Depakote ER, Depakene, Depacon, Depakine, Valparin, Stavzor and Ergenyl. Sodium Valproate is marketed in Sweden as Absenor, Depakine, Orfiril. Valproic acid is marketed in Sweden as Ergenyl and Depakine.

[0017] The steroid to be used in the invention may be selected among the glucocorticoids and includes prednisone, prednisolone, dexamethasone and betamethasone. In one example the HDAC inhibitor is valproic acid and the steroid is prednisone.

The HDAC inhibitor and the steroid may be comprised by a pharmaceutical composition.

Additional ingredients

[0018] The pharmaceutical composition defined above may further comprise one or more other pharmaceutical acceptable pharmaceutical ingredients, such as a pharmaceutically acceptable diluent, carrier, excipient and buffer. "Pharmaceutically acceptable" means a non-toxic compound that does not decrease the effectiveness of the biological activity of the active ingredients. Such pharmaceutically acceptable additives, diluents buffers, carriers or excipients are well-known in the art (see Remington's Pharmaceutical Sciences, 18th edition, A.R Gennaro, Ed., Mack Publishing Company (1990) and handbook of Pharmaceutical Excipients, 3rd edition, A. Kibbe, Ed ., Pharmaceutical Press (2000).

[0019] The term "buffer" is intended to mean an aqueous solution containing an acid-base mixture with the purpose of stabilising pH. Examples of buffering agents are magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-

free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0020] The term "diluent" is intended to mean an aqueous or non-aqueous solution with the purpose of diluting the compounds in the pharmaceutical preparation. The diluent may be one or more of saline, water, polyethylene glycol, propylene glycol or ethanol.

[0021] The excipient may be one or more of carbohydrates, surfactants, polymers, lipids and minerals. Examples of carbohydrates include lactose, sucrose, mannitol, and cyclodextrines, which are added to the composition, e.g., for facilitating lyophilisation. Examples of polymers are starch, cellulose ethers, cellulose carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, ethylhydroxyethyl cellulose, alginates, carageenans, hyaluronic acid and derivatives thereof, polyacrylic acid, polysulphonate, polyethylenglycol/polyethylene oxide, polyethyleneoxide/polypropylene oxide copolymers, polyvinylalcohol/polyvinylacetate of different degree of hydrolysis, and polyvinylpyrrolidone, all of different molecular weight, which are added to the composition, e.g., for viscosity control, for achieving bioadhesion, or for protecting the lipid from chemical and proteolytic degradation. Examples of lipids are fatty acids, phospholipids, mono-, di-, and triglycerides, ceramides, sphingolipids and glycolipids, all of different acyl chain length and saturation, egg lecithin, soy lecithin, hydrogenated egg and soy lecithin, which are added to the composition for reasons similar to those for polymers. Examples of minerals are talc, magnesium oxide, zinc oxide and titanium oxide, which are added to the composition to obtain benefits such as reduction of liquid accumulation or advantageous pigment properties.

[0022] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0023] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

Administration form

[0024] The pharmaceutical formulations may be administered locally or systemically. Routes of administration include topical, ocular, nasal, pulmonar, buccal, parenteral (intravenous, subcutaneous, and intramuscular), oral, vaginal and rectal. Most commonly used being oral administration.

[0025] The pharmaceutical compositions will be administered to a patient in a pharmaceutically effective dose. By "pharmaceutically effective dose" is meant a dose that is sufficient to produce the desired effects in relation to the condition for which it is administered. The exact dose is dependent on the manner of administration, the nature and severity of the disorder. Depending on the general health, sex, age and body weight of the patient different doses may be needed. The administration of the dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals. The active compounds or substances may also be administrated together or separately depending on the administration form.

[0026] Suitable preparation forms are, for example granules, powders, tablets, coated tablets, (micro) capsules, microgranulates effervescent powders or granules, suppositories, injectable solution in ampule form and also preparations with protracted release of active compounds, in whose preparation excipients, diluents or carriers are customarily used as described above. Other preparations may be those which give rise to different release profiles of the active ingredients which are well-known for a person skilled in the art. Examples includes sustained-release, sustained-action, extended-release, time-release or timed-release, controlled-release, modified release, or continuous-release. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently than immediate-release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance(s) (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be excreted later through normal digestion. In some formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface. Micro-encapsulation is also regarded as a more complete technology to produce complex dissolution profiles. Through coating an active pharmaceutical ingredient

around an inert core, and layering it with insoluble substances to form a microsphere it is possible to obtain more consistent and replicable dissolution rates. All of those being well-known for a person skilled in the art.

One example of a preparation form is an effervescent product.

[0027] Effervescence is the reaction (in water) of acids and bases producing carbon dioxide. Examples of acids used in this reaction are citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, acid citrates, succinic acid and mixtures thereof. Citric acid is the most commonly used, and it imparts a citrus-like taste to the product. Examples of bases used in the effervescent reaction are sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, magnesium carbonate, sodium glycocarbonate, carboxylysine and mixtures thereof. Sodium bicarbonate is very common in effervescent formulas.

[0028] The compounds may be mixed together in the effervescent product or alternatively separated from each other. One example being when the two active substances are encapsulated separately from each other and the resulting effervescent product gives rise to different release profiles of the two active substances/ingredients.

The effevervescent product may be in the form of a powder or as a tablet.

[0029] If the product is a tablet it may comprise at least one additive selected from the group comprising binders, lubricants, emulsifiers fillers, surfactants (e.g., polysorbate 80 and sodium lauryl sulfate), flavours, aromas (examples of ingredients giving taste) (such as orange, lemon, bergamon, grapefruit, banana, apricot and strawberry) and colours, including natural or synthetic ones, vitamins, sweeteners (examples of ingredients giving taste) (acesulfame potassium, sodium saccharin, aspartame, stevia and surcalose), nutritional additives (e.g antioxidants, peptides), and mixtures thereof.

[0030] Substances giving taste, colour or antioxidative properties to the effervescent composition can be plant polyphenols coming from natural sources such as blueberries, cranberries, grapes and tea leaves.

[0031] Additionally the tablet may contain various lubricants suitable for use in the composition including water dispersible, water soluble, water insoluble lubricants and combinations thereof. Examples of useful water soluble lubricants include sodium benzoate, polyethylene glycol, L-leucine, adipic acid, and combinations thereof.

[0032] The tablet may also include water insoluble lubricants including, e.g., stearates (e.g., magnesium stearate, calcium stearate and zinc stearate), oils (e.g., mineral oil, hydrogenated and partially hydrogenated vegetable oils, and cotton seed oil) and combinations thereof. The effervescent agent may also comprise vitamins, and minerals.

[0033] The manufacturing process for the production of effervescent products involves some critical steps that need to be addressed carefully during formulation and manufacturing which is well known for a person skilled in the art. Production of effervescent products must occur in very low humidity areas. The best way to produce an effervescent product is in an environment where humidity is under strict control.

[0034] The process of producing tablets, known as "tableting" or "compressing" requires addition of pharmaceutical excipients well known to a person skilled in the art of powders like mixing, granulation and tableting. It is common practice in tablet production to add a lubricant after granulation; the most commonly used substance is magnesium stearate. During effervescent production, substances such as magnesium stearate can generate a problem since they are insoluble in water and, consequently, a film will form on top of the water after the tablet has dissolved. Strategies to overcome this problem are the use of other lubricants that are soluble in water; for example, a mixture of spray dried L-leucine and polyethylene glycol. Alternatively, not using any lubricant has the advantage of avoiding the blending step, but the disadvantage of special requirements for the production.

Amounts and doses

[0035] The HDAC inhibitor will be administrated in different amounts depending on which HDAC inhibitor will be used. This is well known for a person skilled in the art. The same applies for the steroid. The active ingredients could be administrated together or separately. However, below follows a number of examples of amounts that could be utilized. Examples of administration include administration of prednisone or prednisolone in an amount of 20 to 200 mg per day, such as 50-200, 100-150, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170,180, 190 or 200mg Betamethason may be administered in an amount of 4 to 32 mg per day, such as 10-25, 10-20, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 0r 32 mg. Dexamethasone may be administered in an amount of 10 to 80 mg per day, such as 20-70, 10, 20, 30, 40, 50, 60, 70 or 80 mg. Prednisone may be administrated as a single dose or if needed multiple doses.

[0036] The HDAC inhibitor such as Valproic acid may be administrated orally or intravenously in ranges from about 500 mg to about 15000 mg per day, such as from about 4000 mg to about 15000 mg per day, such as from about 400 mg to about 3000 mg per day. For example, oral dosages can be about 800, about 1600, about 2400, about 3000, about

6000, about 9000, about 15000 mg per day. It is understood that the total amount per day can be administered in a single dose or can be administered in multiple dosing such as twice, three, four or five times per day.

[0037] One example of the administration of HDAC inhibitors or pharmaceutically acceptable salts thereof, steroids or pharmaceutically acceptable salts thereof may be that they are administrated alone or in combination at least once daily, such as during morning time, about 5 to 8 in the morning. However, the administration of any of the substances may occur 1, 2, 3, 4 or even up to 5 times daily. Examples of administration include; administration of the HDAC inhibitor three times per day and prednisone once a day. Normally, the steroids are administrated 1-2 times a day depending on the formulation profile and the release profile of the active agent. Administration of the HDAC inhibitor and the steroid may be at least 24- 72 hours prior to said immune and/or chemotherapy, such as 30-60, 40-50 or 48 hours prior to immune and/or chemotherapy and the steroid and the HDAC inhibitor may be administered simultaneously or sequentially. However, the administration may be prior to treatment with chemo- and or immunotherapy but it may also be administrated during or after, but prior to is mandatory.

[0038] The term "treatment" is used in the context of treating a condition, pertains generally to treatment and therapy of a human being in which some desired therapeutic effect is achieved.

[0039] The term treatment also includes other types of treatment and therapies, in which two or more treatments are combined for example simultaneously or sequentially, such as the steroid and the HDAC inhibitor may be administered simultaneously or sequentially. For example the compounds described herein may be used alone or in combination and for example together with other agents, such as cytotoxic agents etc. Examples include chemotherapy (administration of active agents, such as the disclosed compounds or CHOP). CHOP is a combination of cyclophosphamide, doxorubicin, vincristine and prednisone, which may be administrated in amount of 750 +/- 10% mg/m^2 of cyclophosphamide, 50 +/- 10% mg/m^2 of doxorubicin, 1,4 +/- 10% mg/m^2 of vincristine and 50 +/- 10% mg/m^2 of prednisone. Immunotherapy, including antibody, monoclonal antibody or a functional fragment thereof, such as Rituximab,ofatumumab, GA101, tositumumab, ibritumumab, ocraluzumab, veltuzumab, epratuzumab, FTBA05, AME-133V or R603. All the above mentioned antibodies bind to CD20 present on B-cells. The antibodies may be administrated in an amount of 375 +/- 10% mg/m^2. Other examples are prodrugs; surgery, radiation, and gene therapy.

[0040] "Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library. The term antibody as used in this invention is meant to include intact molecules as well as fragments thereof, such as Fab and F(ab').sub.2, Fv and SCA fragments which are capable of binding an epitopic determinant on a protein of interest. A single chain antibody ("SCA") is a genetically engineered single chain molecule containing the variable region of a light chain and the variable region of a heavy chain, linked by a suitable, flexible polypeptide linker.

[0041] The present invention concerns human beings. Thus the methods are applicable to human therapy.

[0042] Following examples are intended to illustrate, but not to limit, the invention in any manner, shape, or form, either explicitly or implicitly.

EXAMPLES

Biological evaluation

[0043] Inventors of the present invention have established a cell line *in vitro* model for CD20antibody-CHOP resistance (CD20 antibody being Rituximab), based on five DLBCL cell lines with differing sensitivity to CD20antibody-CHOP induced cell death *(*Ageberg, Rydström, Lindén, Linderoth, Jerkeman and Drott; Exp Cell Research; May 1;317(8):1179-91*).* In this model, treatment with valproic acid at pharmacological concentrations shows a strong sensitising effect to CHOP mediated cell death. This correlates to an increase in acetylation of histone H3 as measured by western blot analysis. Also, pre-treatment of DLBCL cell lines with a combination of valproic acid and prednisolone for 48 hours further increased their sensitivity to CHOP induced cell death. In addition, also pretreatment with the hydroxamic/carbamic a HDAC inhibitors Trichostatin A and Belinostat sensitized DLBCL cell lines to CHOP-induced cell death, an effect which was potentiated by addition of prednisolone. Moreover, also the steroid dexamethasone potentiated the sensitizing effect to CHOP-induced cell death induced by valproic acid alone. Taken together, the results indicate that a combination of an HDAC inhibitor and a steroid sensitizes Bcell lymphoma cell lines to CHOP-induced cell death. This shows that a combination therapy with an HDAC inhibitor and a steroid will increase the response to chemotherapy or immunochemotherapy in lymphoma treatment.

Example 1

Valproic acid (VPA) sensitises DLBCL cell lines to CHOP treatment.

[0044] The DLBCL cell lines WSU-NHL, Karpas-422, ULA, SU-DHL-5 and SU-DHL-8 cells were treated for 72 hours

with three different concentrations (0.1 mM, 2mM and 10 mM respectively) of valproic acid (VPA) alone, or in combination with CHOP. The CHOP regimen used in all examples consists of 10 μM cyclophosphamide monohydrate, 20 nM doxorubicin hydrochloride, 2 nM vincristine sulfate and 20 μg/ml prednisolone. *(*Ageberg, Rydström, Lindén, Linderoth, Jerkeman and Drott; Exp Cell Research; May 1;317(8):1179-91*).*

[0045] The cell viability was assessed after 72 hours by trypan blue exclusion and normalised to untreated control cells at day 0 (seeding). Data are presented as mean± SEM, n=3.

[0046] As shown in Table 1, addition of valproic acid increased the cell death in response to CHOP treatment in all lymphoma cell lines, shows that a combination of valproic acid and CHOP could be beneficial to lymphoma patients.

Table 1 A: ULA cells

VPA concentration	-CHOP			+CHOP		
	Mean	SEM	N	Mean	SEM	N
Control	100	1	3	66	6	3
0.1 mM	105	1	3	73	3e-001	3
2 mM	52	4	3	52	1	3
10 mM	50	4	3	42	6	3

Table 1 B: Karpas-422 cells

VPA concentration	-CHOP			+CHOP		
	Mean	SEM	N	Mean	SEM	N
Control	101	1	3	81	3	3
0.1 mM	100	2	3	80	1	3
2 mM	102	1	3	67	8	3
10 mM	21	4	3	21	19	3

Table 1C: WSU-NHL cells

VPA concentration	-CHOP			+CHOP		
	Mean	SEM	N	Mean	SEM	N
Control	100	2	3	91	4	3
0.1 mM	99	1	3	63	9	3
2 mM	29	4	3	6	3	3
10 mM	1	1	3	0	0	3

Table 1D: SU-DHL-8 cells

VPA concentration	-CHOP			+CHOP		
	Mean	SEM	N	Mean	SEM	N
Control	102	2	3	64	1	3
0.1 mM	105	2	3	55	5	3
2 mM	67	11	3	0	0	3
10 mM	0	0	3	0	0	3

Table 1E: SU-DHL-5 cells

VPA concentration	-CHOP			+CHOP		
	Mean	SEM	N	Mean	SEM	N
Control	105	5	3	32	1	3
0.1 mM	124	11	3	26	5	3
2 mM	53	2	3	1	1	3
10 mM	0	0	3	0	0	3

Example 2

Physiologically relevant concentrations of Valproic acid (VPA) sensitises DLBCL cell lines to CHOP treatment.

[0047] The DLBCL cell lines SU-DHL-8 (Table 2A) and WSU-NHL (Table 2B) were treated for 72 hours with 0.5 mM or 1.5 mM VPA alone, or in combination with CHOP. The concentration of 0.5 mM VPA was chosen because it is a normal serum concentration during continuous VPA treatment in patients with epilepsy. The concentration of 1.5 mM VPA was chosen because it is the maximal tolerated serum concentration during 5 day VPA treatment for compassionate use as noted by the inventor.

[0048] The cell viability was assessed after 0 (Day 1), 24 (Day 2), 48 (Day 3) and 72 (Day 4) hours respectively, by trypan blue exclusion and normalised to untreated control cells. Data are presented as mean, n=3.

[0049] Treatment effects on viability were tested against the effects of CHOP treatment alone. Significant differences were evaluated using Student's unpaired t-test. All tests were two-sided. Effects were considered statistically significant at $P<0.05$ (*) and $P<0.01$ (**).

[0050] Viability (% of control cells day 1) are shown in Table 2A (SU-DHL-8) and Table 2B (WSU-NHL, n=3) respectively.

[0051] As shown in table 2, physiologically relevant concentrations of VPA increased the cell death in response to CHOP treatment in lymphoma cell lines, showing that a combination of physiologically relevant doses of valproic acid and CHOP could be beneficial to lymphoma patients.

Table 2A

SU-DHL-8	Day 1	Day 2	Day 3	Day 4
Control	100	101	103	97
CHOP	100	96	87	69
0.5 mM VPA	100	102	101	94
1.5 mM VPA	100	97	64	59
0.5 mM VPA + CHOP	100	89	82	49
1.5 mM VPA + CHOP	100	86	35	16

Table 2B

WSU-NHL	Day 1	Day 2	Day 3	Day 4
Control	100	99	100	101
CHOP	100	98	94	86
0.5 mM VPA	100	97	99	98
1.5 mM VPA	100	95	68	36 (**)
0.5 mM VPA + CHOP	100	53	84	57 (*)
1.5 mM VPA + CHOP	100	87	39	27 (*)

Example 3

Valproic acid (VPA) does not interfere with rituximab-mediated cellular cytotoxicity.

[0052] To estimate the impact of VPA on the antibody-dependent-cellular cytotoxicity (ADCC) induced by the CD20 antibody Rituximab.

[0053] WSU-NHL cells (Table 3A and 3B) or SU-DHL-8 cells (Table 3C and 3D) were labelled with PKH26, either left untreated or incubated with 1.5 mM VPA for 24 hours followed by addition of of rituximab at 0, 0,1, or 10 μg/ml

[0054] NK cells were added as an effector to target cell ratio of 10:1, thereafter the cells were incubated for an additional 20 hours. Dead target cells were identified as double positive for PKH26 and 7-AAD and used as readout of the assay. The data shown demonstrate percentage of dead cells, and representative of two independent experiments. The date show that VPA does not affect Rituximab induced ADCC, compatible with the use of VPA together with CD20 antibodies in lymphoma parients.

Table 3A: WSU-NHL cells

Amount of Rituximab (μg/ml)	+NK cells			+NK Cells + 1.5 mM VPA		
	Mean	SEM	N	Mean	SEM	N
0	16	1	6	27	4	7
0.1	35	5	6	40	6	7
1	45	5	6	50	5	7
10	54	2	6	56	3	7

Table 3B: WSU-NHL cells

Amount of Rituximab (μg/ml)	+NK cells + CHOP			+NK Cells + 1.5 mM VPA + CHOP		
	Mean	SEM	N	Mean	SEM	N
0	22	2	5	51	5	5
0.1	45	7	5	60	4	5
1	54	6	5	60	6	5
10	61	5	5	66	3	5

Table 3C: SU-DHL-8 cells

Amount of Rituximab (μg/ml)	+NK cells			+NK Cells + 1.5 mM VPA		
	Mean	SEM	N	Mean	SEM	N
0	30	7	3	34	6	3
0.1	38	4	3	43	8	3
1	50	4	3	49	4	3
10	60	3	3	58	4	3

Table 3D: SU-DHL-8 cells

Amount of Rituximab (μg/ml)	+NK cells + CHOP			+NK Cells + 1.5 mM VPA + CHOP		
	Mean	SEM	N	Mean	SEM	N
0	23	2	3	45	2	4
0.1	38	6	3	50	4	4

(continued)

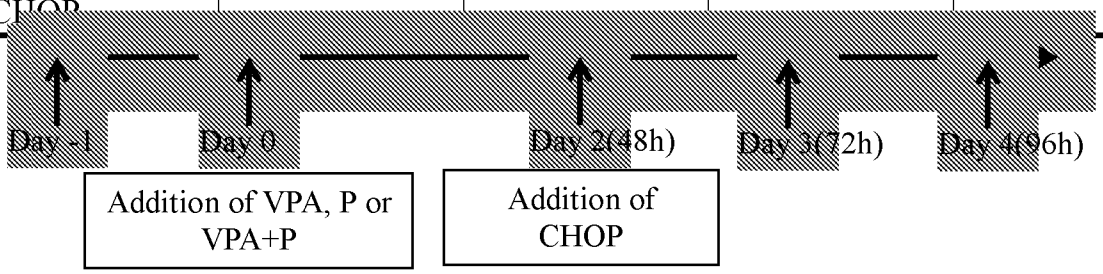
Amount of Rituximab (μg/ml)	+NK cells + CHOP			+NK Cells + 1.5 mM VPA + CHOP		
	Mean	SEM	N	Mean	SEM	N
1	49	7	3	63	2	4
10	59	2	3	66	2	4

Example 4: Pretreatment with Valproic acid (VPA) alone sensitizes DLBCL cell lines to CHOP-treatment. Pretreatment with a combination of VPA and prednisolone significantly increases cell death as compared to pretreatment with VPA alone.

[0055] Pretreatment with VPA before CHOP could theoretically increase the response to CHOP therapy through induction of DNAdamage. However, VPA treatment could result in symptoms such as somnolence in a patient. These symptoms could be counteracted by simultaneous treatment with prednisolone. To study the effect of pretreatment with VPA and prednisolone before CHOP, WSU-NHL cells were treated with different combinations of VPA, prednisolone (P, 20 μg/ml)) and CHOP as illustrated below. Viability was assessed by trypan blue exclusion at indicated time points (n=3). Significant differences were evaluated using Student's unpaired t-test. All tests were two-sided. Effects were considered statistically significant at *P<0.05, **P<0.01, ***P<0.001.

[0056] As shown in table 4, pretreatment with VPA alone sensitizes lymphoma cell lines to CHOP-treatment. Moreover, addition of prednisolone further increases significantly CHOP-induced cell death as compared to pretreatment with VPA alone. These data shows that pretreatment with a combination of VPA and prednisolone before CHOP therapy, will be beneficial to a lymphoma patient.

WSU-NHL	48 h (mean viability/ SEM)	72 h (mean viability/ SEM)	96 h (mean viability/ SEM)	P-value (at 96 h compared to CHOP alone)
Control	99/2	101/1	99/0	0,0213*
0,5 mM VPA	99/1	98/2	97/2	0,0164*
1,5 mM VPA	76/1	65/6	52/7	0,0347*
Prednisolone (P)	97/1	90/3	82/2	0,3143
0,5 mM VPA+P	92/1	78/8	65/8	0,1053
1,5 mM VPA+P	45/10	31/7	18/7	0,0056**
CHOP	99/2	95/2	86/2	-
0,5 mM VPA+CHOP	99/1	97/2	81/1	0,1093
1,5 mM VPA +CHOP	76/1	55/5	40/7	0,0172*
P+CHOP	97/1	85/3	69/6	0,0936
0,5 mM VPA+P+ CHOP	92/1	73/3	55/8	0,0568
1,5 mM VPA+P+ CHOP	45/10	24/4	16/6	0,0034*



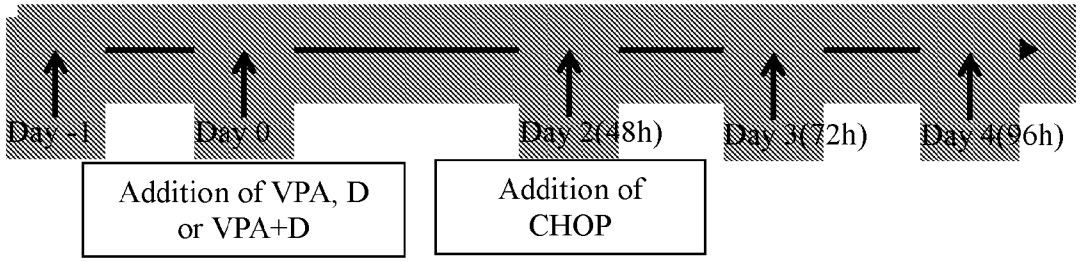
Example 5: Pretreatment with a combination of VPA and the steroid dexamethasone significantly increases CHOP-induced cell death as compared to pretreatment with VPA alone.

[0057] To study whether other steroids than prednisolone could sensitize to the cell death induced by VPA and CHOP, WSU-NHL cells were treated with different combinations of VPA, the steroid dexamethasone (D, 1μM) and CHOP as illustrated below. Viability was assessed by trypan blue exclusion at indicated time points (n=3). Significant differences were evaluated using Student's unpaired t-test. All tests were two-sided. Effects were considered statistically significant at *P<0.05, **P<0.01, ***P<0.001.

[0058] As shown in table 5, pretreament with dexamethasone further increases VPA-CHOP-induced cell death as

compared to pretreatment with VPA alone. These data shows that pretreatment with a combination of VPA and other steroids, such as dexamethasone before CHOP therapy, will be beneficial to a lymphoma patient.

WSU-NHL	48 h (mean viability/ SEM)	72 h (mean viability/ SEM)	96 h (mean viability/ SEM)	P-value (at 96 h compared to CHOP alone)
Control	99/2	101/1	99/0	0,0213*
0,5 mM VPA	99/1	98/2	97/2	0,0164*
1,5 mM VPA	76/1	65/6	52/7	0,0347*
Dexamethasone (D)	92/1	92/3	86/4	0,9507
0,5 mM VPA + D	87/3	79/1	65/6	0,0543
1,5 mM VPA + D	50/7	25/4	18/6	0,0039**
CHOP	99/2	95/2	86/2	-
0,5 mM VPA+CHOP	99/1	97/2	81/1	0,1093
1,5 mM VPA +CHOP	76/1	55/5	40/7	0,0172*
Dexamethasone (D) + CHOP	92/1	85/4	64/3	0,0047**
0,5 mM VPA + D + CHOP	87/3	78/1	58/5	0,0127*
1,5 mM VPA + D + CHOP	50/7	30/6	21/4	0,0003***



Example 6: Pretreatment with the HDACinhibitor Tricostatin A or Belinostat sensitizes DLBCL cell lines to CHOP-treatment. Pretreatment with a combination of Trichostatin A and prednisolone significantly increases CHOP-induced cell death as compared to pretreatment with Trichostatin A or Belinostat alone.

[0059] To study whether pretreatment with HDACinhibitors from other HDACinhibitor subgroups also had a sensitizing

effect to CHOP-induced cell death, WSU-NHL cells were treated with different combinations of the hydroxamic/carbamic acid HDACinhibitor Trichostatin A (TSA) and Belinostat, Prednisolone (P, 20 μg/ml) and CHOP as illustrated below. Viability was assessed by trypan blue exclusion at indicated time points (n=3). Significant differences were evaluated using Student's unpaired t-test. All tests were two-sided. Effects were considered statistically significant at *P<0.05, **P<0.01, ***P<0.001.

[0060] As shown in table 6, pretreatment with Trichostatin A alone sensitizes lymphoma cell lines to CHOP-treatment. Moreover, addition of prednisolone significantly increases CHOP-induced cell death as compared to pretreatment with VPA alone. These data shows that pretreatment with a combination of HDAC inhibitors also from the hydroxamic/carbamic acid group together with prednisolone before CHOP therapy, will be beneficial to a lymphoma patient.

WSU-NHL	48 h (mean viability/ SEM)	72 h (mean viability/ SEM)	96 h (mean viability/ SEM)	P-value (at 96 h compared to CHOP alone)
Control	100/0	100/1	100/0	0,053455053
150 nM TSA	93/2	94/1	97/1	1
300 nM TSA	59/3	42/2	49/1	3,56367E-05***
Prednisolone (P)	99/1	98/0	98/1	0,42039602
150 nM TSA+P	89/5	87/2	87/4	0,121321131
300 nM TSA+P	60/5	36/4	32/4	0,002160384* *
CHOP	100/0	101/0	97/1	-
150 nM TSA+CHOP	93/2	86/3	87/3	0,015277572*
300 nM TSA+CHOP	59/3	45/2	37/7	0,06838847
P+CHOP	99/1	99/2	91/1	0,01151857*
150 nM TSA+P+ CHOP	89/5	78/1	74/2	0,00535689**
300 nM TSA+P+ CHOP	60/5	36/3	24/4	0,001812973**

Belinostat showed similar results (data not shown).

Claims

1. A histone deacetylase (HDAC) inhibitor and a steroid for use in the pretreatment of a disease selected from the group consisting of diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukaemia, T cell lymphoma and Hodgkin lymphoma, wherein the HDAC inhibitor is selected from the group consisting of valproic acid, valproate semisodium, sodium valproate, magnesium valproate or mixtures thereof, and wherein the steroid is selected from the group consisting of prednisone, prednisolone, dexamethasone or betamethasone.

2. A HDAC inhibitor and a steroid for use according to claim 1, wherein the HDAC inhibitor is valproic acid and the steroid is prednisone.

3. A HDAC inhibitor and a steroid for use according to any of claims 1 to 2, wherein the substances are combined in a pharmaceutical composition, wherein the composition is in the form of granulates, powder, tablets, coated tablets, microcapsules, microgranulates or effervescent forms.

4. A HDAC inhibitor and a steroid for use according to claim 3, wherein the substances are in the form of tablets.

5. A HDAC inhibitor and a steroid for use according to any of claims 1 to 2, further in combination with an antibody, monoclonal antibody or functional fragments thereof which binds to CD20

Patentansprüche

1. Histon-Deacetylase(HDAC)-Hemmer und ein Steroid daraus zur Verwendung bei der Vorbehandlung einer Krankheit, die aus der Gruppe ausgewählt ist, die aus diffusem großzelligem B-Zell-Lymphom (DLBCL), follikulärem Lymphom, chronischer lymphatischer Leukämie, T-Zell-Lymphom und Hodgkin-Lymphom besteht, wobei der HDAC-Hemmer aus der Gruppe ausgewählt ist, die aus Valproinsäure, Valproatseminatrium, Natriumvalproat, Magnesiumvalproat oder Mischungen davon besteht, und wobei das Steroid aus der Gruppe ausgewählt ist, die aus Prednison, Prednisolon, Dexamethason oder Betamethason besteht.

2. HDAC-Hemmer und ein Steroid daraus zur Verwendung nach Anspruch 1, wobei der HDAC-Hemmer Valproinsäure ist und das Steroid Prednison ist.

3. HDAC-Hemmer und ein Steroid daraus zur Verwendung nach einem der Ansprüche 1 bis 2, wobei die Substanzen in einer pharmazeutischen Zusammensetzung kombiniert sind, wobei die Verbindung in Form von Granulaten, Pulver, Tabletten, überzogenen Tabletten, Mikrokapseln, Mikrogranulaten oder Brauseformen vorliegt.

4. HDAC-Hemmer und ein Steroid daraus zur Verwendung nach Anspruch 3, wobei die Substanzen in der Form von Tabletten vorliegen.

5. HDAC-Hemmer und ein Steroid daraus zur Verwendung nach einem der Ansprüche 1 bis 2, ferner in Kombination mit einem Antikörper, einem monoklonalen Antikörper oder funktionellen Fragmenten davon, die an CD20 binden.

Revendications

1. Inhibiteur d'histone désacétylase (HDAC) et stéroïde pour une utilisation dans le prétraitement d'une maladie sélectionnée dans le groupe constitué du lymphome diffus à grande cellule B (DLBCL) du lymphome folliculaire, de la leucémie lymphoblastique chronique, du lymphome T et du lymphome hodgkinien, dans lequel l'inhibiteur de HDAC est sélectionné dans le groupe constitué de l'acide valproïque, du valproate hémi-sodique, du valproate de sodium, du valproate de magnésium et de leurs mélanges, et dans lequel le stéroïde est sélectionné dans le groupe constitué de la prednisone, de la prednisolone, de la dexaméthasone ou de la bétaméthasone.

2. Inhibiteur de HDAC et stéroïde pour une utilisation selon la revendication 1, dans lequel l'inhibiteur de HDAC est l'acide valproïque et le stéroïde est la prednisone.

3. Inhibiteur de HDAC et stéroïde pour une utilisation selon l'une quelconque des revendications 1 à 2, dans lequel les substances sont combinées dans une composition pharmaceutique, dans laquelle la composition est sous la forme de granulés, d'une poudre, de comprimés, de comprimés enrobés, de microcapsules, de microgranulés ou sous des formes effervescentes.

4. Inhibiteur de HDAC et stéroïde pour une utilisation selon la revendication 3, dans lequel les substances sont sous la forme de comprimés.

5. Inhibiteur de HDAC et stéroïde pour une utilisation selon l'une quelconque des revendications 1 à 2, en outre en combinaison avec un anticorps, un anticorps monoclonal ou des fragments fonctionnels de ceux-ci qui se lient à CD20.

REFERENCES CITED IN THE DESCRIPTION

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EGY HDAC INHIBITORT ÉS EGY SZTEROIDOT TARTALMAZÓ GYÓGYSZERÉSZETI KÉSZÍTMÉNY ÉS ENNEK ALKALMAZÁSA

Igénypontok

1. Egy hiszton-deacetiláz (HDAC) inhibitor és egy szteroid, amelyet a diffúz nagy B-sejtes limfóma (DLBCL), a follikuláris limfóma, a krónikus limfocitás leukémia, a T-sejtes limfóma és a Hodgkin-limfóma csoportjából kiválasztott betegség előkezelésére használnak, ahol a HDAC inhibitor a valproinsav, a valproát szeminátrium, a nátrium-valproát, a magnézium-valproát vagy ezek keverékei, és ahol a szteroid a prednizon, a prednizolon, a dexametazon vagy a betametazon csoportjából van kiválasztva.

2. Az 1. igénypont szerinti alkalmazásra szolgáló HDAC-inhibitor és szteroid, ahol a HDAC-inhibitor valproinsav és a szteroid prednizon.

3. Az 1-2. igénypontok bármelyike szerinti alkalmazásra szolgáló HDAC-inhibitor és szteroid, ahol az anyagokat egy gyógyszerészeti készítményben kombinálják, ahol a készítmény granulátumok, porok, tabletták, bevont tabletták, mikrokapszulák, mikrogranulátumok vagy pezsgőformák alapjában van kialakítva.

4. A 3. igénypont szerinti alkalmazásra szolgáló HDAC-inhibitor és szteroid, ahol az anyagok tabletták formájában vannak jelen.

5. Az 1-2. igénypontok bármelyike szerinti alkalmazásra szolgáló HDAC-inhibitor és szteroid, amely továbbá egy antitesttel, monoklonális antitesttel vagy utóbbiak funkcionális fragmenseivel van kombinálva, amelyek a CD20-hoz kötődnek.