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(57) Abrégé/Abstract:
The invention relates to the use of at least one human recombinant histone, especially at least one histone H1 subtype, and/or a therapeutic histone fraction as a basis for the treatment of thrombocytopenia.

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(54) Title: USE OF HISTONES FOR THERAPEUTIC PURPOSES

(54) Bezeichnung: VERWENDUNG VON HISTONEN ZU THERAPEUTISCHEN ZWECKEN

(57) Abstract: The invention relates to the use of at least one human recombinant histone, especially at least one histone H1 subtype, and/or a therapeutic histone fraction as a basis for the treatment of thrombocytopenia.

(57) Zusammenfassung: Die Erfindung betrifft die Verwendung wenigstens eines humanen rekombinanten Histons; insbesondere wenigstens eines Histon H1-Subtyps, und/oder eines therapeutisch wirksamen Histonabschnittes als Basis zur therapeutischen Behandlung von Thrombozytopenie.

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USE OF HISTONES TO TREAT THROMBOCYTOPENIA

Field of Invention

The invention relates to the use of at least one human recombinant histone of H1 subtype and/or of its therapeutically effective segment, especially histone H1.3 for therapeutic purposes.

Background

The use of therapeutic active substances based on human recombinant histone H1 subtypes for the treatment of cancers, e.g. leukemia, is disclosed in the article by Reiner Class et al. in Am. J. Clin. Oncol. (CCT) vol. 19 No. 5 1996 and European patent publication 973,541.

The effect of histone H1 and H2A/H2B fractions from calf thymus on hematopoietical stem cells (CFU-S) in normal and radioactively irradiated rats was described in a Russian article by Semina O.V. et al. in Radiatsionnaia Biologiia, Radioecologiia 34 (4-5), 1994, Jul.-Oct.

In complex pathological conditions such as acute myeloid leukemia, there is frequently observed to be a thrombocytopenia which may even be enhanced by a chemotherapeutic treatment of the leukemia. Thrombocytopenia is, however, also observed with other etiology. Since thrombocytopenia may lead to life-threatening internal hemorrhages, therapies for various pathological symptoms which may be the cause of the thrombocytopenia are frequently made particularly difficult.

Summary of the Invention

It was therefore an object of the invention to find an active substance which can be used therapeutically for thrombocytopenia in order thus also to improve substantially the success of curing the basic symptom as inducer of the thrombocytopenia.

It has been possible according to the invention to achieve thè object by using for the therapy of thrombocytopenia inter alia as a result of faulty stem cell differentiation or weakened proliferation of megakaryocytes an active substance based on at least one human recombinant histone (especially at least one histone of H1 subtype) and/or its therapeutically effective segment.

This applies especially to a thrombocytopenia as concomitant manifestation of a hematological disorder.

It is moreover possible to employ the therapeutic method of the invention for the treatment of thrombocytopenia during or after chemotherapy for the treatment of a hematological disorder, especially acute myeloid leukemia.

It has surprisingly been possible to show that the active substance of the invention shows on the one hand a positive result in the treatment of a hematological disorder such as leukemia, but on the other hand also a positive result in the treatment of the thrombocytopenia associated with the hematological disorders.

It was thus possible with one and the same active substance to note both a regression in the leukemia and an increase in platelets.

Description of Drawing

Figure 1 is a graphical representation of the number of platelets in the peripheral blood of a patient treated with H1.3 at various time intervals during and after treatment.

Detailed Description of the Invention

It was possible to achieve therapeutic trial results also on patients with human recombinant histone H1.3, it having been possible to reduce markedly the number of pathological tumor cells in an AML patient and, at the same time, to increase substantially platelet production, whereby it was possible to improve substantially the prospects of curing the patient.

The trial results are reproduced in more detail below, the active substance used in this case, based on human

recombinant H1.3 concentrations 37.5 mg/qm^2 of body surface area etc., having been administered in a 0.9% NaCl solution intravenously 3 times a week over a period of about 4 hours.

The effect of the active substances of the invention in a 0.9% NaCl solution at 37.5 mg/qm^2 of body surface area on the thrombocytopenia of a patient is shown in the appended diagram.

The platelets in peripheral blood are on the ordinate in a number of from 0 to 40 x 10^9. Treatment with active substance of the invention for three weeks is shown on the abscissa, the platelet count measured for the patient before the first treatment being greatly reduced at about 8 x 10^9. Then in each case three drip infusions take place per week with in each case 4 hours per infusion, with the 1st to 3rd infusion on the 1st, 3rd and 5th day in the first week, with the 4th to 6th infusion on the 8th, 10th and 12th day in the second week and finally with the 7th to 9th infusion on the 15th, 17th and 19th day in the 3rd week. On the 29th day after the first infusion, a control measurement of the platelet count took place without a further infusion with the active substance of the invention. At a later time FU1, the patient was discharged with an almost normal platelet count of about 34 x 10^9, without an active substance of the invention having been supplied even once. This value lay outside the need to supply stored blood. The patient was asked to attend a follow-up examination with the possibility of resumption of treatment if the platelet count has not improved further on its own or had even deteriorated. The results of the follow-up examination are not shown here.

The appended diagram shows at the start of the second week up to conclusion of the treatment in the third week a jump in the platelet count after the 5th day of

treatment and then a continuous rise in the platelet count from the 8th to the subsequent 19th day of treatment and a further slower rise in the platelet count at the first control examination on the 29th day and at a later discharge day FU1 of the patient without further addition of the active substance of the invention, the finally measured platelet count being, as already stated, about 32.5×10^9.

The invention is not restricted to the use of human recombinant H1.3. Because of the close relationship of the H1 subtypes, it is obvious to a skilled worker also to employ as active substance other human recombinant H1 subtypes as basis for the active substance of the invention.

Following the successful therapy of patients with a thrombocytopenia, here as concomitant syndrome of an AML leukemia, with human recombinant histone H1.3, it is particularly obvious to a skilled worker also to employ other recombinant H1 subtypes as alternative active substances singly or in combination according to the invention.

The active substance of the invention preferably consists of the complete unshortened subtypes of histone proteins. However, it is also obvious to a skilled worker to look for the therapeutically effective segment, of which he is capable directly on the basis of his expert knowledge and experience without outstanding innovative contributions being necessary in this case. Such therapeutically effective histone segments therefore lie within the range of equivalents of the teaching of the invention disclosed herein.

The invention further discloses the therapeutic teaching of employing, when there is a threatening or incipient primary disorder which, experience has shown,

may result in thrombocytopenia, the active substance of the invention prophylactically against a threatening thrombocytopenia even if, unlike leukemia, the active substance of the invention is not effective against the primary disorder.

CLAIMS:

1. Use of human recombinant histone H1 to treat thrombocytopenia in a patient.

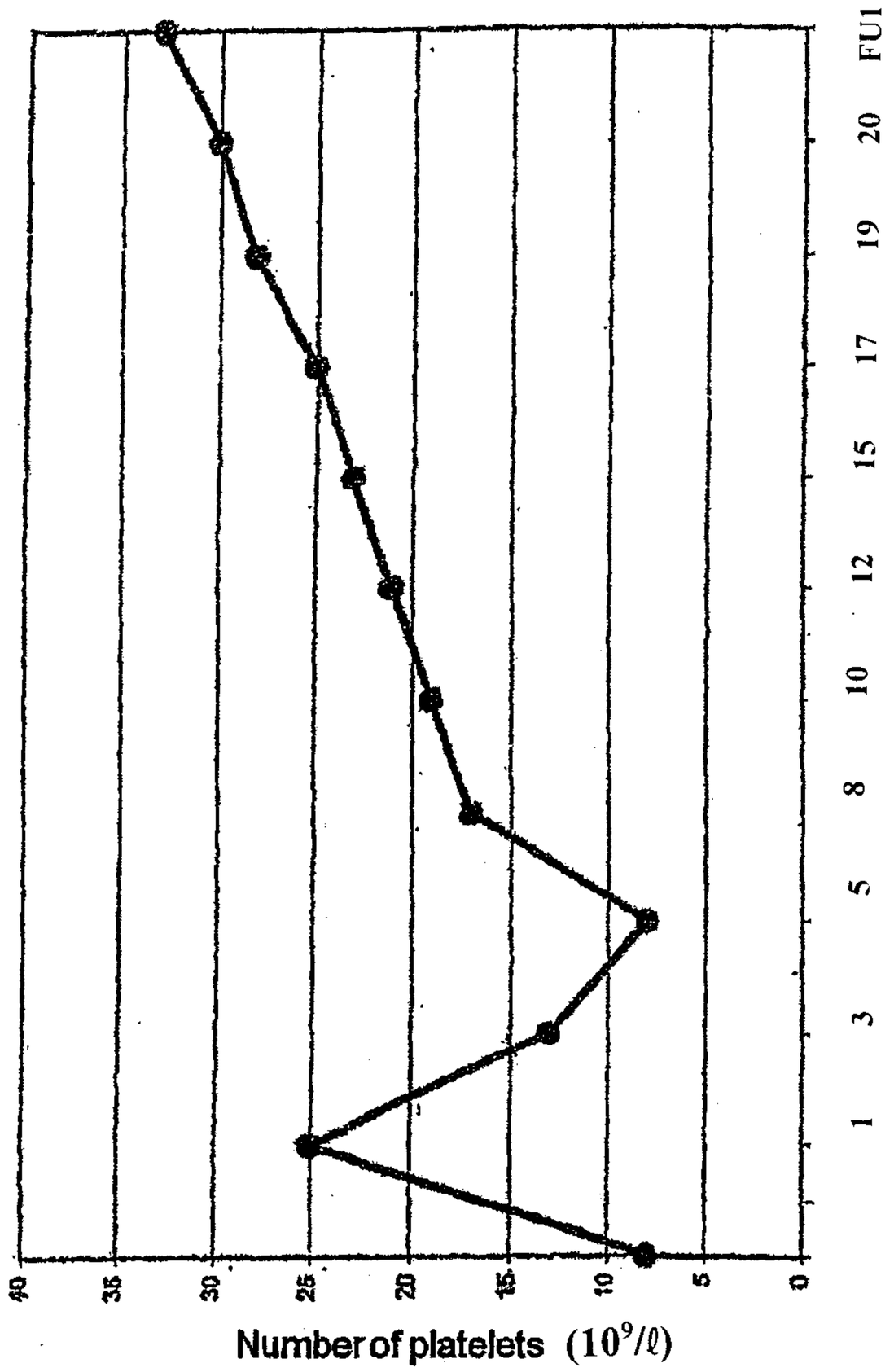
2. The use of Claim 1 wherein the use occurs during or after chemotherapy.

3. The use of Claim 1 or 2 wherein the histone H1 is subtype histone H1.3.

4. The use of Claim 1 or 2 wherein the histone H1 is in a 0.9% NaCl solution at a concentration of 37.5 mg/qm^2 based on the body surface area of the patient.

5. The use of Claim 3 wherein the histone H1.3 is in a 0.9% NaCl solution at a concentration of 37.5 mg/qm^2 based on the body surface area of the patient.

FIG. 1


Number of platelets ($10^9/\ell$)
40
35
30
25
20
15
10
5
0
Days after treatment with H1.3
1
3
5
8
10
12
15
17
19
20
FU1