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(54) **Homoharringtonine alone or combined with other agents for use in treating chronic myelogenous leukemia resistant or intolerant to protein kinase inhibitors other than STI 571**

Homoharringtonine allein oder in Kombination mit anderen Substanzen zur Anwendung zur Behandlung von chronischer myelogenischer Leukemia resistent oder intolerant gegenüber Proteinkinasehemmern ausgenommen STI 571

Homoharringtonine seule ou en combinaison avec d'autres agents pour une utilisation dans le traitement des leucémies myélogènes chroniques résistantes ou intolérantes aux inhibiteurs de protéine kinase à l'exception du STI 571

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Description

[0001] The invention relates to methods for treating subjects suffering from chronic myelogenous leukemia which is resistant or intolerant to treatment with protein kinase inhibitors other than ST1571, involving treating the subjects with homoharringtonine alone or combined with protein kinase inhibitors other than STI571 and/or other antileukemic agents.

[0002] Chronic myelogenous leukemia (CML) is a myeloproliferative disease which strikes about 4,500 new cases per year in the U.S. or in Europe. The median survival of this disease is around 3 years without treatment. Since the introduction of standard therapy by interferon alpha (INF) the median survival of this leukemia reaches about 7 years. However when patients become resistant to interferon, progression to acute phases occurs. Until these recent years there were only a few drugs able to induce a new remission. [Ref 1-5] Homoharringtonine, an alkaloid isolated from the genus *Cephalotaxus* [Ref 1, 2, 6, 7] and more recently STI571, a synthetic product, are recent drugs able to give a new remission to patients resistant to INF. Moreover STI571 was recently approved in the U.S. as major therapy of CML.

[0003] STI571 is becoming the standard of therapy, for CML; recent clinical studies indicate that good results are obtained in patients with chronic phase CML: > 90% of complete hematologic response, including 50% of cytogenetic response. However, limited result are seen in accelerated phase (< 40%), and poor efficacy is obtained in blastic phase (< 10% of complete hematologic response) including very transient remission. [Ref 8] In addition, after 15 months on STI571, we recently found that actuarial risk or progression to accelerated phase or blastic phase was higher than 30% [Ref 9] (unpublished results). To overcome these therapeutic limitations, combinations of STI571 with existing standard therapy based on INFs (including new form of INF such as PEG INF) were recently tried. Preliminary analysis of these combinations indicates that addition of INF or PEG INF does not change really the efficacy of each drug given alone. [Ref 9] (unpublished results)

[0004] There is therefore a need for improved methods of treating CML which provide longer term remission. In view of the limitations of STI571, there is a need for therapies providing improved results in the treatment of accelerated phase CML and blastic phase.

[0005] The article of Bell Beverly A et al, Medical and Pediatric Oncology, US, vol. 37, n°2, 1 august 2001, pages 103-107-XP009131071 describes the use of homoharringtonine to patients suffering from acute myelogenous leukemia who are resistant to other antileukemic agents. However, the nature of the antileukemic agents is not specified. The patients were enrolled in the study disclosed in this document between 1987 and 1993. The first protein kinase inhibitor was not approved until 2001.
The article of Feldman et al, Database Biosis (Online) Biosciences Information Service, Philadelphia, PA, US, 1992, XP002574542 & Leukemia (Basingstoke) vol. 6, n°11, 1992, pages 1185-1188 describes the use of homoharringtonine to treat acute myelogenous leukemia into patients primarily resistant to cytarabine. Cytarabine is not a protein kinase inhibitor.
The article of O'Brien et al, Blood, vol. 86, n°9, 1 November 1995, pages 3322-3326, XP002574544 describes the use of homoharringtonine to treat chronic myelogenous leukemia in patients primarily resistant to interferon. Interferon is not a protein kinase inhibitor.
The article of Warrell R P JR et al, Database Biosis (Online) Biosciences Information Service, Philadelphia, PA, US, 1985 XP002574543 & Journal of Clinical Oncology, Vol. 3, n°5, 1985, pages 617-621, describes the use of homoharringtonine to treat acute non lymphoblastic leukemia in patients previously resistant to conventional chemotherapy. However, the conventional chemotherapy is not specified. This article has been published in 1985 and at that date no protein kinase inhibitors were approved for acute myelogenous leukemia.
The article of Robin Jean-Pierre et al, Blood, American Society of Hematology, US, n°11, Part 1, 16 November 2000, page 306A, XP009131188 describes the use of homoharringtonine to treat chronic myelogenous leukemia in patients primarily resistant to interferon. Interferon is not a protein kinase inhibitor.

[0006] It was recently published that STI571 and homoharringtonine combination exhibit additive or synergistic cytotoxic effect in vitro, [Ref 10-13] which allows their clinical use as combination. In another preliminary study, it was indicated that homoharringtonine exhibits activity in a standard myeloid cell line made resistant in vitro to STI571.

[0007] We discovered recently that cells coming from patients with chronic myelogenous leukemia resistant to STI571, exhibited a good sensibility to homoharringtonine. [14] (unpublished results). We also found that patients resistant or intolerant to STI571 exhibit hematologic response to homoharringtonine, and furthermore that this response is sometimes transient (Robin JP et al., unpublished results). This finding could be explained by the rapid appearance of new malignant clones in which an alternate mechanism of apoptosis inhibition was "found" by a mutation-selection process of leukemic cells.

[0008] Further support for such a mechanism can be found in recent articles which indicate that the two drugs induce a release of the inhibition of caspase (a key molecular signal in the triggering of apoptosis) according two different alternative pathways:

- First, for homoharringtonine, independent of reactive oxygen species (ROS) generation; [Ref 15]
- Second, for STI, ROS dependent; [Ref 16]

In addition, Ara-C, a fourth agent currently combined with both INF, homoharringtonine and more recently STI571, induce apoptosis according to a ROS dependent mech-

anism [Ref 17]. (Some findings indicate that interferon alpha cytotoxicity would act according to a ROS dependent mechanism [Ref 18]).

[0009] This indicates that homoharringtonine may be use as new treatment of patients resistant to CML but also that standard methods of treatment which includes removing the existing resistant therapy and replace it by the new putatively active one should by improved.

[0010] The present invention is based on the discovery that the treatment of CML using the combination of STI571 and homoharringtonine resulted in improved treatment outcomes, and that treatment with homoharringtonine results in effective treatment of CML which is resistant or intolerant to STI571. The invention is also based on the discovery that treatment of CML using first STI571 and then homoharringtonine in the absence of STI571 may lead to a transient response.

[0011] The invention provides a novel method of treatment of patients with chronic myelogenous leukemia, other related myeloproliferative diseases and Ph-positive acute lymphocytic leukemia involving homoharringtonine based therapy in order to overcome primary or secondary resistance and/or intolerance to protein kinase inhibitors other than STI571, and able to induce or to improve hematologic response and/or cytogenetic response and, eventually, survival, with a mild non hematologic toxicity. Homoharringtonine is preferably combined with one or more other antileukemic agents including protein, kinase inhibitors other than STI571 itself. In other embodiments, homoharringtonine is combined simultaneously with one or more other antileukemic agents including protein kinase inhibitors other than STI571 itself which is continued. In other aspects, homoharringtonine can be combined sequentially with one or more other antileukemic agents, optionally protein kinase inhibitors other than STI571 itself which is continued. In other aspects of these methods, homoharringtonine can be combined sequentially by addition to existing protein kinase inhibitors other than STI571 therapy including in patients who lost their response to or who failed to respond to this agent in using the following steps (a) to (d), optionally (e): (a) patients with chronic myelogenous leukemia, eventually resistant to standard interferon alpha therapy, are treated by protein kinase inhibitors other than STI571 (400 to 800 mg daily, permanently) until a complete cytogenetic response (for de novo patients) or at least a complete hematologic response (for all other more advanced phases) are obtained, (b) in these partially protein kinase inhibitors other than STI571-resistant patients, protein kinase inhibitors other than STI571 is not removed but only reduced to 300 to 400 mg daily, in those of patients who failed to have or lost their complete cytogenetic or hematologic response, (c) homoharringtonine is administered subcutaneously and/or intravenously or/and orally, at dose 0.25 to 5 mg/m^2, preferably at dose 2.5 mg/m^2, preferably for 2 to 14 days per 28-day cycle, (d) finally homoharringtonine dose and/or protein kinase inhibitors other than STI571 are adjusted according to cytopenia and/or side effects; and (e) optionally, subcutaneous or intravenous or oral nucleoside synergistic with homoharringtonine, preferably cytarabine may be simultaneously or sequentially added to homoharringtonine,

[0012] The present invention concerns a method of treating chronic myelogenous leukemia, a related myeloproliferative disorder or a Ph-positive acute lymphocytic leukemia in a subject animal, comprising:

(a) selecting or identifying an animal suffering from chronic myelogenous leukemia or a related myeloproliferative disorder and showing resistance or intolerance to treatment with protein kinase inhibitors other than STI571; and
(b) administering to the animal homoharringtonine.

[0013] The present invention further relates to a method of treating chronic myelogenous leukemia or a related myeloproliferative disorder in a subject animal, comprising (a) selecting or identifying an animal suffering from chronic myelogenous leukemia or a related myeloproliferative disorder or Ph-positive acute lymphocytic leukemia and showing resistance or intolerance to treatment with protein kinase inhibitors other than STI571; and (b) administering to the animal homoharringtonine in an amount effective to inhibit proliferation of myeloid cells. In certain embodiments, homoharringtonine and protein kinase inhibitors other than STI571 and/or other antileukemic agents are administered in combination, more preferably homoharringtonine is added to a therapeutic regimen comprising protein kinase inhibitors other than STI571 without discontinuing the protein kinase inhibitors other than STI571 treatment. In other embodiments homoharringtonine and protein kinase inhibitors other than STI571 and/or other antileukemic agents are administered in a sequential treatment.

[0014] In a preferred embodiment, the homoharringtonine is combined with one or more other antileukemic agents including protein kinase inhibitors other than_ STI571 Preferably, homoharringtonine is combined simultaneously with one or more other antileukemic agents including protein kinase inhibitors other than STI571. More preferably, homoharringtonine is combined simultaneously with one or more other antileukemic agents including protein kinase inhibitors other than STI571, wherein protein kinase inhibitors other than STI571 is continued from previous treatment.

In another preferred embodiment, homoharringtonine is combined sequentially with one or more other antileukemic agents. Preferably, homoharringtonine is combined sequentially with one or more other antileukemic agents including protein kinase inhibitors other than STI571 itself which is continued.

[0015] The present invention also embodies a method for inhibiting proliferation of a hyperproliferative myeloid cell, as well as to a method of treating CML or a related myeloproliferative disorder in a subject animal, compris-

ing: a) contacting said cell with or administering to said animal protein kinase inhibitors other than STI571; and b) contacting said cell with, or administering to said animal, homoharringtonine. Accordingly, the invention also relates to a method of preventing resistance to protein kinase inhibitors other than STI571, in a subject animal suffering from CML or a related myeloproliferative disorder. In further preferred embodiments, the methods of the invention further comprise treating said hyperproliferative myeloid cell or animal with one or more other therapeutic antileukemic compounds, preferably in sequential treatment, Several examples of suitable compounds are further mentioned herein. The protein kinase inhibitors other than STI571 and homoharringtonine will preferably be administered in an amount effective to inhibit proliferation of myeloid cells,

[0016] Therefore, the present invention concerns also a method of treatment, wherein homoharringtonine is combined sequentially by addition to existing protein kinase inhibitors other than STI571 therapy, including in patients who lost their response to or who failed to respond to protein kinase inhibitors other than STI571, comprising the following steps (a) to (d), and optionally (e):

(a) administering to patients with chronic myelogenous leukemia, optionally resistant to standard interferon alpha therapy, protein kinase inhibitors other than STI571 (preferably at 400 to 800 mg daily, permanently) until a complete cytogenetic response (preferably for de novo patients) or at least a complete hematologie response (preferably for all other more advanced phases) is obtained,

(b) in these partially protein kinase inhibitors other than STI571-resistant patients, reducing to 300 to 400 mg daily but not removing protein kinase inhibitors other than STI571 treatment, in those patients who failed to have or lost their complete cytogenetic or hematologic response,

(c) administering homoharringtonine subcutaneously and/or intravenously or/and orally, at dose 0.25 to 5 mg/m^2, preferably at dose 2.5 mg/m^2, preferably for 2 to 14 days per 28-day cycle;

(d) adjusting the homoharringtonine dose and/or protein kinase inhibitors other than STI571 dose according to cytopenia and/or side effects;

(e) optionally, subcutaneously or intravenously administering an oral nucleoside synergistic with homoharringtonine, wherein said oral nucleoside may be added simultaneously or sequentially to homoharringtonine.

In a preferred embodiment, said oral nucleoside in step (e) is cytarabine, wherein cytarabine may be added simultaneously or sequentially to homoharringtonine.

[0017] In another embodiment, the present invention concerns a method for inhibiting proliferation of a hyperproliferative myeloid cell resistant to protein kinase inhibitors other than STI571, comprising:

a) contacting the cell with protein kinase inhibitors other than STI571; and

b) contacting the cell with homoharringtonine,

wherein STI571 and homoharringtonine are provided in an amount effective to inhibit proliferation of said myeloid cell.

[0018] In a further embodiment, the present invention concerns a method of treating chronic myelogenous leukemia, a related myeloproliferative disorder or a Ph-positive acute lymphocytic leukemia in a subject animal:

a) administering to the animal in a first course of treatment protein kinase inhibitors other than STI571,wherein said CML or disorder displays resistance and/or intolerance to protein kinase inhibitors other than STI571;

b) administering to the animal a second course of treatment a combination of homoharringtonine and protein kinase inhibitors other than STI571 in an amount effective to inhibit proliferation of myeloid cells.

[0019] The (hyperproliferative) myeloid cell or myeloproliferative disorder will preferably be characterized as being resistant and/or intolerance to protein kinase inhibitors other than STI571, that is, protein kinase inhibitors other than STI571 when not combined with homoharringtonine. Preferably the efficacy of the therapy is enhanced through synergistic effects of protein kinase inhibitors other than STI571 and homoharringtonine.

[0020] Preferably the treatment of the present invention is able to overcome resistance and/or intolerance to protein kinase inhibitors other than STI571.

[0021] More preferably said treatment induces a hematologic response, and/or a cytogenetic response and/or survival, with weak non-hematologic toxicity.

[0022] In a preferred embodiment the efficacy of the therapy is enhanced through synergistic effects of protein kinase inhibitors other than STI571 and homoharringtonine.

[0023] Preferably, the other antileukemic agents are interferon alpha and/or one or more nucleosides and/or farnesyl transferase inhibitor (FTI).

[0024] More preferably, the other antileukemic agent is interferon alpha or PEG-interferon,

[0025] More preferably, the other antileukemic agent agent is a nucleoside. More preferably, the nucleosides are cytarabine (Ara-C) and/or decitabine and/or troxacytabine. More preferably, the nucleoside is cytarabine (Ara-C).

[0026] More preferably, the other antileukemic agents is a farnesyl transferase inhibitors (FTT).

[0027] More preferably, the other agents are a combination of interferon alpha and cytarabine.

In a preferred embodiment, the animal treated by the

treatment of the present invention is a human being,

[0028] The present invention also concern the use of Homoharringtonine with other chemotherapeutic agent, in particular protein kinase inhibitors other than STI571, as a combined preparation for simultaneous, separate or sequential use in CML therapy or for treating a related myeloproliferative disorder, advantageously for treating CML or a related myeloproliferative disorder in an animal, advantageously a human being, showing resistance or intolerance to treatment with protein kinase inhibitors other than STI571.

[0029] As mentioned, protein kinase inhibitors other than STI571 and homoharringtonine can be administered during the same course or cycle of treatment. In one embodiment they can be coadministered, optionally substantially simultaneously, optionally as a single pharmaceutical composition. The methods of the invention may also involve the administration of protein kinase inhibitors other than STI571 and homoharringtonine to an animal such as a human patient who has not been previously treated with protein kinase inhibitors other than STI571. Preferably, however, the protein kinase inhibitors other than STI571 and homoharringtonine are administered to an animal which has undergone a first course or cycle of therapy for the treatment of the myeloproliferative disorder. In related aspects, the inventions also comprise methods of treatments where more than one course of therapy is carried out. Included is a method of treating CML or a related myeloproliferative disorder or Ph-positive acute lymphocytic leukemia in a subject animal comprising: a) administering to the animal in a first course or cycle of treatment protein kinase inhibitors other than STI571; and b) administering to the animal in a second course or cycle of treatment a combination of homoharringtonine protein kinase inhibitors other than STI571 in an amount effective to inhibit proliferation of the cell. Generally this method will be used when said subject shows resistance or intolerance to treatment with protein kinase inhibitors other than STI571 in the first course or cycle of treatment.

[0030] Said other antileukemic agents that can be used in therapeutic combinations of the invention with homoharringtonine may include interferon alpha (including interferon alpha or PEG-interferon) and/or one or more nucleosides (including cytarabine (Ara-C) and/or decitabine and/or troxacytabine) and/or a farnesyl transferase inhibitor (FTI). In preferred embodiments of the methods of treatment, the other agents are combination of interferon alpha and cytarabine.

[0031] While reference is generally made to STI571 which is currently commercially available as an approved pharmaceutical product, and for which particularly surprising results were obtained using the methods of the invention, it will be appreciated that the invention also applies to other related agents, including other protein kinase inhibitors, more preferably protein tyrosine kinase inhibitors such as Bcr-Abl kinase inhibitors, or more preferably other compounds of the 2-phenylaminopyrimidine type.

[0032] Advantageously, Homoharringtonine is administrated by subcutaneous administration such as described in the patent application US 09/801 751. Advantageously, Homoharringtonine is administrated in the form of a salt such as described in the patent application US 09/801 751.

[0033] The invention is illustrated by way of the following figures:

Figure 1 is a plan of an example of single arm studies of the sequential addition of HHT in patients in an ongoing treatment with STI571 for chronic phase (CP), accelerated phase (AP) or blastic phase (BP) of CML, who lost or failed to have a major hematologic response.

Figure 2 is a graph of the white-blood cell (WBC) count over time in the case of a patient treated by homoharringtonine plus cytarabine during a one year period after a severe intolerance to STI571: La Roche-Sur-Yon; Patient # 14, Tar. Fr., .F, Age 43; Accelerated phase Chronic Myelogenous Leukemia, (Diagn.: > 15% Peripheral, Resistant. To INF+Ara-C, HU, BCNU then Serious Hepatic Cytolysis Under STI51). White Blood Cell count Follow-up

Figure 3 is a graph of the white blood cell (WBC) count over time in the case of a patient successively resistant to five drugs including STI571, treated by homoharringtonine: Patient # 15, MG, M, Age 44, treated with homoharringtonine. Chronic Phase CML. (Diagn.: Resistant To INF 5MU/Day+Ara-C 200mg/m2/D; HU. Farnesyl transferase inhibitor (FTI); then STI571 at 600 mg then 800mg/day: hematologic failure). WBC Count Follow-up

Figure 4 is a plan of a multicenter Phase III controlled study of addition of HHT to existing STI571. therapy, in patients with CP of CML who lost or failed to have complete cytogenetic response (CGR), under STI571 therapy.

Figure 5 is a plan of a multicenter Phase II single arm study of sequential addition of HHT, in patients with an ongoing treatment by STI571 for AP of CML, who lost or failed to have a major hematologic response.

[0034] The main aspect of this invention describes a new method of therapy based on treatment with homoharringtonine and its combination with protein kinase inhibitors other than STI571 plus eventually a third drug such as Ara-C and plus eventually a fourth drug such as interferon alpha, in order to induce a remission or to improve the existing level of hematologic and/or cytogenetic response and, finally, survival in patients (in particular human) with chronic myelogenous leukemia, or with oth-

er related myeloprolyferative disease or with Ph-positive acute lymphocytic leukemia who lost their response with or who failed to respond to or are intolerant protein kinase inhibitors other than ST1571.

[0035] Moreover, this invention describes a new regimen of use of homoharringtonine based on sequential addition of homoharringtonine to existing treatment based protein kinase inhibitors other than STI571 plus eventually another drug such as interferon alpha and/or Ara-C, without stopping existing treatment for which the patient is resistant, able to induce a new remission or to improve the existing level of hematologic and/or cytogenetic response in patients with chronic myelogenous leukemia who failed to have or who lost or decreased their level of hematologic and/or cytogenetic responses to the said existing treatment.

[0036] Also, this invention describes a new method of therapy, based on homoharringtonine sequential substitutive combinations of protein kinase inhibitor other than STI571 able to induce a new remission in patients with chronic myelogenous leukemia who failed to have or who lost biological and/or clinical response.

[0037] We discovered that leukemic cells of patients with blast crisis of chronic myelogenous leukemia who relapse after treatment by STI571 or other protein kinase inhibitors are sensitive to homoharringtonine: there is no cross resistance between homoharringtonine and STI571 or other protein kinase inhibitors.

[0038] In addition, we selected two STI571-resistant cell lines in order to analysis the combination of the two drugs: K562-s and LAMA84-s, two human cell lines exhibiting the feature of chronic myelogenous leukemia. The effect of homoharringtonine was also determined in their STI571-resistant counterparts K-562-r and LAMA84-r, respectively. Homoharringtonine was apparently additive if not mildly antagonistic in K562-s and LAMA84-s, but, surprisingly clearly synergistic in their STI571-resistant counterparts K-562-r and LAMA84-r (see table II of Example 2). In other word, the more a cell line is resistant, the more the addition of homoharringtonine to existing STI571 is synergistic. This observation is unexpected because usually synergistic effect is not related with cross-resistance. The consequence of this observation is one of the key aspects of our invention: homoharringtonine-protein kinase inhibitors such as STI571 combination is more efficient in patients resistant to protein kinase inhibitors such as ST1571 than is patient sensible to this product and this efficacy will be higher if protein kinase inhibitors such as STI571 is maintained during the homoharringtonine administration.

[0039] The following method of therapy is used:

- patients with chronic myelogenous leukemia resistant or not to standard interferon based therapy are treated by protein kinase inhibitors other than STI571 until complete hematologic response is obtained;
- then, those of patients who failed to have or lost their hematologic response are treated by homoharingtonine in using the usual regimen (2.5 mg/m^2, 5 to 7 days per 28-day cycle) but contrary to the usual practice in chemotherapy, the first drug for which the patient is partially resistant (protein kinase inhibitors others than STI571) is not removed to allow to the synergistic effect to occur;
- then those patients who failed to have or lost their hemalologic response may be treated by a third agent, preferably cytarabine(Ara-C).

[0040] This new sequential additive methods of therapy is able to give a large rate of complete hematologic response and the resulting median survival would reach a time never encountered prior to the present invention, hematologic response and the resulting medal survival would reach a time never encountered.

[0041] "Cell proliferative disorders" refer to disorders wherein unwanted cell proliferation of one or more subset (s) of cells in a multicellular organism occurs, resulting in harm (e.g., discomfort or decreased life expectancy) to the multicellular organism. Cell proliferative disorders can occur in different types of animals and in humans. Among cell proliferative disorders are myeloproliferative disorders such as CML.

[0042] A "therapeutic effect" generally refers to either the inhibition, to some extent, of growth of cells causing or contributing to a cell proliferative disorder. A therapeutic effect relieves to some extent one or more of the symptoms of a cell proliferative disorder. In reference to the treatment of a myeloproliferative disorder, a therapeutic effect can include but is not limited to one or more of the following: 1) reduction in the number of cancer (e.g. leukemia) cells; 2) hematologic response; 3) cytogenetic response; and/or 4) relieving to some extent one or more of the symptoms associated with the disorder.

[0043] The compounds of this invention can be administered to a patient alone, or in a pharmaceutical composition comprising the active compound and a carrier or excipient. Formulations, dosages, and methods of administration for the preferred compounds individually will already be available, e.g. the widespread commercial use of STI571, and previous studies conducted with homoharringtonine, and methods of administration can be carried out using any suitable manner known in the art, or as described in the examples. Nevertheless, the compounds or pharmaceutical compositions can be administered by different routes, in different formulations or dosage, etc. including but not limited to intravenously, subcutaneously, orally or topically.

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Claims

1. Homoharringtonine for use in the treatment of chronic myelogenous leukemia, a related myeloproliferative disorder or a Ph-positive acute lymphocytic leukemia in a subject animal showing resistance or intolerance to treatment with protein kinase inhibitors other than STI571.

2. Homoharringtonine for use according to claim 1 wherein homoharringtonine is combined with one or more other antileukemic agents including protein kinase inhibitors other than STI571.

3. Homoharringtonine for use according to any of claims 1 or 2 in which homoharringtonine is administered simultaneously with one or more other antileukemic agents including protein kinase inhibitors other than STI571.

4. Homoharringtonine for use according to claim 3 wherein protein kinase inhibitor other than STI571 is continued from previous treatment.

5. Homoharringtonine for use according to claim 2 in which homoharringtonine is administered sequentially with one or more other antileukemic agents other than STI571.

6. Homoharringtonine for use according to claim 5 in which homoharringtonine is administered sequentially with one or more other antileukemic agents including protein kinase inhibitors other than STI571 which is continued.

7. Homoharringtonine for use according to claim 6, wherein homoharringtonine is administered sequentially by addition to existing protein kinase inhibitors other than STI571 therapy, including to patients who lost their response to or who failed to respond to protein kinase inhibitors other than STI571, according to the following steps (a) to (d), and optionally (e):

   (a) administering to patients with chronic myelogenous leukemia, optionally resistant to standard interferon alpha therapy, protein kinase inhibitors other than STI571, until a complete cy-

togenetic response, or at least a complete hematologic response, is obtained,
(b) in these partially protein kinase inhibitors other than STI571-resistant patients, reducing to 300 to 400 mg daily but not removing protein kinase inhibitors other than STI571 treatment, in those patients who failed to have or lost their complete cytogenetic or hematologic response,
(c) administering homoharringtonine subcutaneously and/or intravenously or/and orally, at dose 0.25 to 5 mg/m^2,
(d) adjusting the homoharringtonine dose and/or protein kinase inhibitors other than STI571 dose according to cytopenia and/or side effects;
(e) optionally, subcutaneously or intravenously administering orally a nucleoside synergistic with homoharringtonine, wherein said nucleoside may be added simultaneously or sequentially to homoharringtonine.

8. Homoharringtonine for use according to claim 7, wherein said oral nucleoside in step (e) is cytarabine, wherein cytarabine may be added simultaneously or sequentially to homoharringtonine.

9. A combined preparation of homoharringtonine and protein kinase inhibitors other than STI571 for simultaneous, separate or sequential use, intended for inhibiting proliferation of a hyperproliferative myeloid cell resistant to protein kinase inhibitors other than STI571, wherein:

the cell are first contacted with protein kinase inhibitors other than STI571 before being contacted with homoharringtonine,
and wherein protein kinase inhibitors other than STI571 and homoharringtonine are provided in an amount effective to inhibit proliferation of said myeloid cell.

10. A combined preparation of homoharringtonine and protein kinase inhibitors other than STI571 for simultaneous, separate or sequential use, intended for treating chronic myelogenous leukemia, a related myeloproliferative disorder or a Ph-positive acute lymphocytic leukemia in a subject animal displaying resistance and/or intolerance to protein kinase inhibitors other than STI571 after a first course of treatment with protein kinase inhibitors other than STI571 wherein the preparation is administered to the patient in a second course of treatment in an amount effective to inhibit proliferation of myeloid cells.

11. Homoharringtonine for use according to Claims 1 to 6, which is able to overcome resistance and/or intolerance to protein kinase inhibitors other than STI571.

12. Homoharringtonine for use according to Claims 1 to 6, which induces a hematologic response, and/or a cytogenetic response and/or survival, with weak non-hematologic toxicity.

13. Homoharringtonine for use according to Claim 2 wherein the efficacy thereof is enhanced through synergistic effects of protein kinase inhibitors other than STI571 and homoharringtonine.

14. Homoharringtonine for use according to claims 2 to 6 in which the other antileukemic agents are interferon alpha and/or one or more nucleosides and/or a farnesyl transferase inhibitor (FTI).

15. Homoharringtonine for use according to claim 6 in which the other antileukemic agents is interferon alpha or PEG-interferon.

16. Homoharringtonine for use according to claim 6 in which the other antileukemic agents is a nucleoside.

17. Homoharringtonine for use according to claim 14 in which the other antileukemic agents is a farnesyl transferase inhibitor (FTI).

18. Homoharringtonine for use according to claim 16 in which the nucleosides are cytarabine (Ara-C) and/or decitabine and/or troxacytabine.

19. Homoharringtonine for use according to claim 18 in which a nucleoside is cytarabine (Ara-C).

20. Homoharringtonine for use according to claim 14 in which the other agents are a combination of interferon alpha and cytarabine.

21. Homoharringtonine for use according to one of the precedent claims wherein the animal is a human being.

22. Homoharringtonine for use according to one of the precedent claims wherein protein tyrosine kinase inhibitors other than STI571 are Bcr-Ab1 kinase inhibitors other than STI571.

23. Homoharringtonine for use according to one of the precedent claims wherein protein kinase inhibitors other than STI571 are of the 2-phenylaminopyrimidine type.

Patentansprüche

1. Homoharringtonin zur Verwendung in der Behandlung von chronischer myeloischer Leukämie, einer verwandten myeloproliferativen Erkrankung oder einer Ph-positiven akuten lymphozytischen Leukämie bei einem tierischen Lebewesen, das Resistenz

oder Unverträglichkeit gegen die Behandlung mit Proteinkinasehemmern mit Ausnahme von STI571, zeigt.

2. Homoharringtonin zur Verwendung nach Anspruch 1, wobei Homoharringtonin mit einem oder mehreren antileukämischen Mitteln kombiniert wird, einschließlich Proteinkinasehemmern mit Ausnahme von STI571.

3. Homoharringtonin zur Verwendung nach einem der Ansprüche 1 oder 2, wobei Homoharringtonin gleichzeitig mit einem oder mehreren anderen antileukämischen Mitteln, einschließlich Proteinkinasehemmern mit Ausnahme von STI571, verabreicht wird.

4. Homoharringtonin zur Verwendung nach Anspruch 3, wobei ein Proteinkinasehemmer mit Ausnahme von STI571, von einer vorhergehenden Behandlung fortgesetzt wird.

5. Homoharringtonin zur Verwendung nach Anspruch 2, wobei Homoharringtonin sequenziell mit einem oder mehreren antileukämischen Mitteln mit Ausnahme von STI571, verabreicht wird.

6. Homoharringtonin zur Verwendung nach Anspruch 5, wobei Homoharringtonin sequenziell mit einem oder mehreren antileukämischen Mitteln, einschließlich Proteinkinasehemmern mit Ausnahme von STI571, die fortgesetzt werden, verabreicht wird.

7. Homoharringtonin zur Verwendung nach Anspruch 6, wobei Homoharringtonin sequenziell verabreicht wird durch Zugabe zu einer bestehenden Therapie mit Proteinkinasehemmern mit Ausnahme von STI571, einschließlich an Patienten, welche ihr Ansprechen auf Proteinkinasehemmer mit Ausnahme von STI571, verloren haben oder welche nicht darauf angesprochen hatten, entsprechend den folgenden Schritten (a) bis (d) und wahlweise (e):

(a) Verabreichung an Patienten mit chronischer myeloischer Leukämie, wahlweise resistent gegen standardmäßige Therapie mit Interferon Alpha, Proteinkinasehemmern mit Ausnahme von STI571, bis ein vollständiges zytogenetisches Ansprechen oder zumindest ein vollständiges hämatologisches Ansprechen erzielt wird,
(b) bei diesen teilweise gegen Proteinkinasehemmer mit Ausnahme von STI571, resistenten Patienten Reduktion auf 300 bis 400 mg täglich aber nicht Absetzen der Behandlung mit Proteinkinasehemmern mit Ausnahme von STI571, bei jenen Patienten, welche kein vollständiges zytogenetisches oder hämatologisches Ansprechen zeigten oder es verloren,
(c) Verabreichung von Homoharringtonin subkutan und/oder intravenös und/oder oral in einer Dosis von 0,25 bis 5 mg/m^2,
(d) Anpassen der Dosis von Homoharringtonin und/oder der Proteinkinasehemmer mit Ausnahme von STI571, in Abhängigkeit von der Zytopenie und/oder von Nebenwirkungen;
(e) wahlweise, subkutane oder intravenöse oder orale Verabreichung eines Nucleosids, das synergistisch mit Homoharringtonin ist, wobei dieses Nucleosid gleichzeitig mit oder sequenziell zu Homoharringtonin verabreicht werden kann.

8. Homoharringtonin zur Verwendung nach Anspruch 7, wobei das orale Nucleosid in Schritt (e) Cytarabin ist, wobei Cytarabin gleichzeitig mit oder sequenziell zu Homoharringtonin verabreicht werden kann.

9. Ein kombinierte Zubereitung aus Homoharringtonin und Proteinkinasehemmern mit Ausnahme von STI571, zur gleichzeitigen, getrennten oder sequenziellen Verwendung, vorgesehen zur Hemmung der Proliferation einer hyperproliferativen myeloiden Zelle, die gegen Proteinkinasehemmer mit Ausnahme von STI571, resistent ist, wobei:

die Zelle zuerst mit Proteinkinasehemmern mit Ausnahme von STI571, in Kontakt gebracht wird, bevor sie mit Homoharringtonin in Kontakt gebracht wird,
und wobei Proteinkinasehemmer mit Ausnahme von STI571, und Homoharringtonin in einer Menge vorliegen, die ausreicht, um die Proliferation der myeloiden Zelle zu hemmen.

10. Eine kombinierte Zusammensetzung von Homoharringtonin und Proteinkinasehemmern mit Ausnahme von STI571, zur gleichzeitigen, getrennten oder sequenziellen Verwendung, vorgesehen zur Behandlung von chronischer myeloischer Leukämie, einer verwandten myeloproliferativen Krankheit oder einer Ph-positiven akuten lymphozytischen Leukämie bei einem tierischen Lebewesen, das nach einer ersten Behandlungsphase mit Proteinkinasehemmern mit Ausnahme von STI571, Resistenz und/oder Unverträglichkeit gegenüber Proteinkinasehemmern mit Ausnahme von STI571, aufweist, wobei die Zubereitung dem Patienten in einer zweiten Behandlungsphase in einer Menge verabreicht wird, die ausreicht, um die Proliferation von myeloiden Zellen zu hemmen.

11. Homoharringtonin zur Verwendung nach den Ansprüchen 1 bis 6, das die Resistenz und/oder Unverträglichkeit gegenüber Proteinkinasehemmern mit Ausnahme von STI571, überwinden kann.

12. Homoharringtonin zur Verwendung nach den An-

sprüchen 1 bis 6, das ein hämatologisches Ansprechen und/oder ein zytogenetisches Ansprechen und/oder Überleben hervorruft, bei geringer nichthämatologischer Toxizität.

13. Homoharringtonin zur Verwendung nach Anspruch 2, wobei die Wirksamkeit davon durch synergistische Wirkungen von Proteinkinasehemmern mit Ausnahme von STI571, und Homoharringtonin verstärkt wird.

14. Homoharringtonin zur Verwendung nach den Ansprüchen 2 bis 6, wobei die anderen antileukämischen Mittel Interferon Alpha und/oder ein oder mehrere Nucleoside und/oder ein Farnesyltransferasehemmer (FTI) sind.

15. Homoharringtonin zur Verwendung nach Anspruch 6, wobei die anderen antileukämischen Mittel Interferon Alpha oder PEG-Interferon sind.

16. Homoharringtonin zur Verwendung nach Anspruch 6, wobei die anderen antileukämischen Mittel ein Nucleosid sind.

17. Homoharringtonin zur Verwendung nach Anspruch 14, wobei die anderen antileukämischen Mittel ein Farnesyltransferasehemmer (FTI) sind.

18. Homoharringtonin zur Verwendung nach Anspruch 16, wobei die Nucleoside Cytarabin (Ara-C) und/oder Decitabin und/oder Troxacytabin sind.

19. Homoharringtonin zur Verwendung nach Anspruch 18, wobei ein Nucleosid Cytarabin (Ara-C) ist.

20. Homoharringtonin zur Verwendung nach Anspruch 14, wobei die anderen Mittel eine Kombination von Interferon Alpha und Cytarabin sind.

21. Homoharringtonin zur Verwendung nach einem der vorhergehenden Ansprüche, wobei das Lebewesen ein Mensch ist.

22. Homoharringtonin zur Verwendung nach einem der vorhergehenden Ansprüche, wobei Proteintyrosinkinasehemmer ausgenommen STI571 Bcr-Abl-Kinasehemmer mit Ausnahme von STI571, sind.

23. Homoharringtonin zur Verwendung nach einem der vorhergehenden Ansprüche, wobei Proteinkinasehemmer mit Ausnahme von STI571, vom Typ 2-Phenylaminopyrimidin sind.

Revendications

1. Homoharringtonine pour une utilisation dans le traitement de la leucémie myéloïde chronique, d'un syndrome myéloprolifératif lié ou d'une leucémie aiguë lymphoblastique à Ph positif sur un sujet animal présentant une résistance ou une intolérance au traitement avec des inhibiteurs de protéine kinase différents du STI571.

2. Homoharringtonine pour une utilisation selon la revendication 1, dans lequel l'homoharringtonine est combiné avec un ou plusieurs autres agents anti-leucémiques comprenant les inhibiteurs de protéine kinase différents du STI571.

3. Homoharringtonine pour une utilisation selon l'une quelconque des revendications 1 ou 2, dans lequel l'homoharringtonine est administré simultanément avec un ou plusieurs autres agents anti-leucémiques comprenant les inhibiteurs de protéine kinase différents du STI571.

4. Homoharringtonine pour une utilisation selon la revendication 3, dans lequel on continue de prendre l'inhibiteur de protéine kinase différent du STI571 depuis le précédent traitement.

5. Homoharringtonine pour une utilisation selon la revendication 2, dans lequel l'homoharringtonine est administré de manière séquentielle avec un ou plusieurs autres agents anti-leucémiques différents du STI571.

6. Homoharringtonine pour une utilisation selon la revendication 5, dans lequel l'homoharringtonine est administré de manière séquentielle avec un ou plusieurs autres agents anti-leucémiques comprenant les inhibiteurs de protéine kinase différents du STI571 dont la prise est poursuivie.

7. Homoharringtonine pour une utilisation selon la revendication 6, dans lequel l'homoharringtonine est administré de manière séquentielle en plus de la thérapie existante par les inhibiteurs de protéine kinase différents du STI571, comprenant les patients qui ont perdu leur réponse aux inhibiteurs de protéine kinase différents du STI571 ou qui n'arrivent pas à répondre aux inhibiteurs de protéine kinase différents du STI571, selon les étapes suivantes (a) à (d), et facultativement (e), consistant à :

(a) administrer aux patients souffrant d'une leucémie myéloïde chronique, facultativement résistants à la thérapie à base d'interféron alpha standard, les inhibiteurs de protéine kinase différents du STI571, jusqu'à ce qu'une réponse cytogénétique complète, ou au moins une réponse hématologique complète, soit obtenue,
(b) chez ces patients partiellement résistants aux inhibiteurs de protéine kinase différents du

STI571, réduire à 300 à 400 mg par jour, mais sans arrêter le traitement par les inhibiteurs de protéine kinase différents du STI571, chez ces patients qui n'arrivent pas à avoir ou perdent leur réponse cytogénétique ou hématologique complète,
(c) administrer l'homoharringtonine par voie sous cutanée et/ou par voie intraveineuse et/ou par voie orale, à une dose de 0,25 à 5 mg/m^2,
(d) ajuster la dose d'homoharringtonine et/ou la dose d'inhibiteurs de protéine kinase différents du STI571 selon la cytopénie et/ou les effets secondaires ;
(e) facultativement, administrer par voie sous cutanée ou par voie intraveineuse un nucléoside oral synergique avec l'homoharringtonine, dans lequel ledit nucléoside oral peut être ajouté simultanément ou de manière séquentielle à l'homoharringtonine.

8. Homoharringtonine pour une utilisation selon la revendication 7, dans lequel ledit nucléoside oral à l'étape (e) est la cytarabine, dans lequel la cytarabine peut être ajoutée de manière simultanée ou de manière séquentielle à l'homoharringtonine.

9. Préparation combinée d'homoharringtonine et d'inhibiteurs de protéine kinase différents du STI571 pour une utilisation simultanée, séparée ou séquentielle, destinée à empêcher la prolifération d'une cellule myéloïde hyper prolifération résistante aux inhibiteurs de protéine kinase différents du STI571, dans laquelle :

les cellules sont tout d'abord en contact avec les inhibiteurs de protéine kinase différents du STI571, avant d'être en contact avec l'homoharringtonine,
et dans laquelle les inhibiteurs de protéine kinase différents du STI571 et l'homoharringtonine sont prévus selon une quantité efficace pour empêcher la prolifération de ladite cellule myéloïde.

10. Préparation combinée d'homoharringtonine et d'inhibiteurs de protéine kinase différents du STI571 pour une utilisation simultanée, séparée ou séquentielle, destinée au traitement de la leucémie myéloïde chronique, d'un syndrome myéloprolifératif lié ou d'une leucémie aiguë lymphoblastique à Ph positif sur un sujet animal présentant une résistance et/ou une intolérance aux inhibiteurs de protéine kinase différents du STI571 après un premier traitement avec les inhibiteurs de protéine kinase différents du STI571 dans laquelle la préparation est administrée à un patient lors d'un second traitement selon une quantité efficace pour empêcher la prolifération des cellules myéloïdes.

11. Homoharringtonine pour une utilisation selon les revendications 1 à 6, qui peut venir à bout de la résistance et/ou de l'intolérance aux inhibiteurs de protéine kinase différents du STI571.

12. Homoharringtonine pour une utilisation selon les revendications 1 à 6, qui induit une réponse hématologique et/ou une réponse cytogénétique et/ou la survie avec une faible toxicité non hématologique.

13. Homoharringtonine pour une utilisation selon la revendication 2, dans lequel l'efficacité de celui-ci est accrue par le biais des effets synergétiques des inhibiteurs de protéine kinase différents du STI571 et de l'homoharringtonine.

14. Homoharringtonine pour une utilisation selon les revendications 2 à 6, dans lequel les autres agents anti-leucémiques sont l'interféron alpha et/ou un ou plusieurs nucléosides et/ou un inhibiteur de farnésyltransférase (FTI).

15. Homoharringtonine pour une utilisation selon la revendication 6, dans lequel les autres agents anti-leucémiques sont l'interféron alpha ou le PEG interféron.

16. Homoharringtonine pour une utilisation selon la revendication 6, dans lequel les autres agents anti-leucémiques sont un nucléoside.

17. Homoharringtonine pour une utilisation selon la revendication 14, dans lequel les autres agents anti-leucémiques sont un inhibiteur de farnésyltransférase (FTI).

18. Homoharringtonine pour une utilisation selon la revendication 16, dans lequel les nucléosides sont la cytarabine (Ara-C) et/ou la décitabine et/ou la troxacitabine.

19. Homoharringtonine pour une utilisation selon la revendication 18, dans lequel un nucléoside est la cytarabine (Ara-C).

20. Homoharringtonine pour une utilisation selon la revendication 14, dans lequel les autres agents sont une combinaison d'interféron alpha et de la cytarabine.

21. Homoharringtonine pour une utilisation selon l'une des revendications précédentes, dans lequel l'animal est un être humain.

22. Homoharringtonine pour une utilisation selon l'une des revendications précédentes, dans lequel les inhibiteurs de la protéine tyrosine kinase différents du STI571 sont des inhibiteurs de Ber-Abl kinase diffé-

rents du STI571.

23. Homoharringtonine pour une utilisation selon l'une des revendications précédentes, dans lequel les inhibiteurs de la protéine tyrosine kinase différents du STI571 sont de type 2-phénylamino-pyrimidine.

REFERENCES CITED IN THE DESCRIPTION

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