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(54) Titre : TRAITEMENT DES METASTASES ET DU CANCER
(54) Title: TREATMENT OF TUMOR METASTASES AND CANCER

(57) Abrégé/Abstract:
Tumor metastases in cancer patients are inhibited by administration of a combination therapy including effective amounts of Interleukin-2 and a methylol transfer agent such as taurolidine, taurultam or mixtures thereof.

ABSTRACT OF THE DISCLOSURE

Tumor metastases in cancer patients are inhibited by administration of a combination therapy including effective amounts of Interleukin-2 and a methylol transfer agent such as taurolidine taurultam or mixtures thereof.

TREATMENT OF TUMOR METASTASES AND CANCER

Field of the Invention

The present invention relates to the field of treating tumor metastases and cancer.

Description of the Background Art

Interleukin-2 (IL-2) is an agent which has been suggested for inhibiting tumor cell growth. However, administration of IL-2 to patients presents severe toxicity problems, since IL-2 elicits an extremely strong systemic inflammatory response syndrome (SIRS) reaction in patients. Toxicity of IL-2 is so severe that approximately 70% of patients cannot tolerate treatment.

Additionally, a common problem in patients undergoing cancer treatment is tumor recurrence or metastasis.

Thus, despite the advances in cancer treatment, there remains a significant need in the art for new and improved cancer treatment therapies.

SUMMARY OF THE INVENTION

In accordance with the present invention, tumor metastasis is inhibited in a cancer patient by administering to said patient a combination therapy comprising effective amounts of IL-2 and a methylol transfer agent.

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that methylol transfer agents such as taurolidine and taurultam reduce or substantially eliminate the severe toxicity and side effects of IL-2 in a combination therapy for inhibiting tumor metastases and treating cancer in patients, while it has unexpectedly been found that the efficacy of IL-2 is actually enhanced by the methylol transfer agents in the combination therapy of the present invention.

IL-2 when used in accordance with the present invention includes natural or recombinant Interleukin-2, or biologically active derivatives or substantial equivalents thereof.

Methylol transfer agents include methylol-containing compounds such as taurolidine and taurultam. The compounds taurolidine and taurultam are disclosed in U.S. Patent No. 5,210,083. Other suitable methylol-containing compounds may be found among those identified in PCT Publication No. WO 01/39763. Particularly preferred methylol transfer agents for utilization in accordance with the present invention are taurolidine, taurultam, biologically active derivatives thereof and mixtures thereof.

Particularly preferred embodiments involve treatment of cancers selected from the group consisting of malignant melanoma and renal cancer, and inhibition of tumor metastases thereof. For example, the combination therapy of the present invention has been found to be particularly effective in inhibiting metastatic malignant melanoma and metastatic renal cell carcinoma.

Other cancers to which the combination therapy of the present invention is effective may include other carcinomas, sarcomas or lymphomas. Cancers to which the present invention may be applicable include glioma, neuroblastoma, astrocytoma, carcinomatous meningitis, breast cancer, ovarian cancer, colon cancer, prostate cancer, pancreatic cancer, central nervous system (CNS) cancer, liver cancer, lung cancer, gastric cancer, esophageal cancer, urinary bladder cancer, leukemia, lymphoma, melanoma, renal cell cancer and metastases thereof.

Effective daily dosage amounts of IL-2 may comprise pharmaceutical dosage units within the range of 1,000,000-100,000,000 units (U) IL-2 per m^2 body surface area. Dosage amounts of IL-2 also may be found within the range of 100,000-1,000,000 U per kilogram body weight. Dosage amounts of IL-2 further may be found within the range of 0.1-100 micrograms IL-2 per kilogram body weight.

Effective dosage amounts of a methylol transfer agent in accordance with the present invention may comprise pharmaceutical dosage units within the range of about 0.1-1,000 mg/kg. Preferred dosages may be in the range of about 10-20 grams taurolidine, taurultam or a mixture thereof, per administration.

Pharmaceutical dosage units of the combined therapy of the present invention may be administered by any suitable route, which include oral, topical or peritoneal administration, e.g., subcutaneously, intraperitoneally, intramuscularly, or intravenously, e.g., by infusion or injection.

In preferred embodiments, 250 ml of taurolidine 2% solution is administered by intravenous infusion about 1-6 times per day, more preferably about 2-4 times per day, during a treatment period, concurrently with administration of about 10,000,000-40,000,000 units m^2 IL-2 by intravenous infusion per day during the treatment period.

The present invention also is directed to a combination of IL-2 and a methylol transfer agent, in effective amounts for simultaneous, separate or sequential use for inhibiting tumor metastasis in a cancer patient. The invention also is directed to pharmaceutical combinations including pharmaceutical dosage units comprising effective amounts of Interleukin-2 and a methylol transfer agent for inhibiting tumor metastasis in a cancer patient, as well as to pharmaceutical compositions comprising such combinations.

The invention is further illustrated by the following non-limiting examples.

Example 1

A 63 year old patient diagnosed with metastatic malignant melanoma was treated as follows.

Presentation	Right supra-clavicular mass. Originally had nodular melanoma excised from right elbow, and had high-dose interferon post-operatively. Required axillary clearance for a mass in right axilla eight months later. Further staging was clear at that time. Presented one year later with a fixed inoperable mass in right supra-clavicular area.
Treatment	IL-2 and Taurolidine
Regimen	Interleukin-2 Day 1: 18 million units/m^2 IL-2 infusion over 6 hours Day 2: 18 million units/m^2 IL-2 infusion over 12 hours Day 3: 18 million units/m^2 IL-2 infusion over 24 hours Days 4-7: 18 million units/m^2 IL-2 infusion over 78 hours Taurolidine Taurolidine 2% 250 ml infusion over twelve hours, daily during IL-2 administration Completed five courses of the above

After one year, the patient is alive and well, with no evidence of disease on imaging.

Example 2

A 50 year old patient diagnosed with metastatic renal cell carcinoma was treated as follows.

	Presentation	Haemoptysis - 2° to pulmonary metastases. Noted to have hepatic metastases, in addition to a large mass in the left kidney.
	Treatment Regimen	IL-2 and Taurolidine Interleukin-2 Day 1: 18 million units/m^2 IL-2 infusion over 6 hours Day 2: 18 million units/m^2 IL-2 infusion over 12 hours Day 3: 18 million units/m^2 IL-2 infusion over 24 hours Days 4-7: 18 million units/m^2 IL-2 infusion over 78 hours Taurolidine Taurolidine 2% 250 ml infusion over two hours, twice daily during IL-2 administration Completed five courses of the above
	Further treatment	Left radical nephrectomy

After five years, the patient is alive and well, with no evidence of disease on imaging.

Example 3

A male patient who had recurrent nodular melanoma after interferon treatment was subsequently treated with Interleukin-2 and Taurolidine as follows:

Presentation	Recurrence of nodular melanoma lesion in right shoulder.
Treatment	IL-2 and Taurolidine

Regimen	<u>Interleukin-2</u> Day 1: 36 million units/m^2 IL-2 infusion over 6 hours Day 2: 36 million units/m^2 IL-2 infusion over 12 hours Day 3: 36 million units/m^2 IL-2 infusion over 24 hours Days 4-7: 36 million units/m^2 IL-2 infusion over 78 hours <u>Taurolidine</u> Taurolidine 2% 250 ml infusion over twelve hours, sequentially with IL-2 administration, during days 1-6 Undertook five courses -- during second course, treatment was interrupted and stopped at 78 hours, and during the fifth course, treatment was interrupted during day 4.

Follow-up CT scans indicated a reduction in the size of the lesion, and subsequently indicated no evidence of disease.

CLAIMS

1. The use of a methylol transfer agent selected from taurolidine, taurultam, or a combination thereof, in the manufacture of a preparation for reducing toxicity and side effects of IL-2 in treatment of cancer in a cancer patient.

2. The use of claim 1 wherein said taurolidine, taurultam or combination thereof enhances efficacy of said IL-2.

3. The use of claim 1 wherein said taurolidine, taurultam or combination thereof is in an amount equivalent to about 0.1-1000 mg/kg patient body weight.

4. The use of claim 1 wherein said taurolidine is in an amount of about 10-20 mg.

5. The use of claim 1 wherein said taurolidine is in an amount of about 250 ml 2% by weight taurolidine solution.

6. The use of claim 1 wherein said cancer is glioma, neuroblastoma, astrocytoma, carcinomatous meningitis, breast cancer, ovarian cancer, colon cancer, prostate cancer, pancreatic cancer, liver cancer, lung cancer, gastric cancer, esophageal cancer, urinary bladder cancer, leukemia, lymphoma, melanoma, renal cell cancer or metastases thereof.

7. The use of claim 6 wherein said cancer is melanoma.

8. The use of claim 6 wherein said cancer is metastatic malignant melanoma.

9. The use of claim 6 wherein said cancer is metastatic renal cell carcinoma.

10. The use of claim 1 wherein said taurolidine, taurultam or a combination thereof is in an amount of 5 g.

11. The use of claim 1 wherein said taurolidine, taurultam or a combination thereof is in an amount of 10 g.

12. Use of interleukin-2 (IL-2) and a toxicity-reducing amount of a methylol transfer agent selected from taurolidine, taurultam and a mixture thereof in the manufacture of a combination medicament for reducing the toxicity or toxic side effects of IL-2 during administration of IL-2 to a patient for treatment of a cancer or cancer metastasis, wherein said medicament is prepared for simultaneous, separate or sequential administration to the cancer patient.

13. The use of claim 12 wherein said cancer is a lymphoma, carcinoma or sarcoma.

14. The use of claim 12 wherein said cancer is a glioma, a neuroblastoma, an astrocytoma, carcinomatous meningitis, breast cancer, ovarian cancer, colon

cancer, prostate cancer, pancreatic cancer, liver cancer, lung cancer, gastric cancer, esophageal cancer, urinary bladder cancer, leukemia, melanoma, and renal cell cancer.

15. The use of claim 12 wherein said tumor metastasis is metastatic malignant melanoma or metastatic renal cell carcinoma.

16. Use of IL-2 and a toxicity-reducing amount of a methylol transfer agent selected from taurolidine, taurultam and a mixture thereof in the manufacture of a combination medicament for reducing the toxicity or toxic side effects of IL-2 during administration of IL-2 to a patient for treatment of renal cancer or malignant melanoma, wherein said medicament is prepared for simultaneous, separate or sequential administration to the cancer patient.

17. A combination comprising Interleukin-2 (IL-2) and a methylol transfer agent selected from taurolidine, taurultam and a mixture thereof, in effective amounts for simultaneous, separate or sequential use for reducing the toxicity or toxic side effects of IL-2 during administration of IL-2 to a cancer patient for treatment of a cancer or cancer metastasis.

18. The combination of claim 17 wherein said IL-2 and said methylol transfer agent are each present as a separate pharmaceutical dosage unit.

19. A pharmaceutical combination comprising each of the pharmaceutical dosage units of claim 18 for use in reducing the toxicity or toxic side effects of IL-2 during administration of IL-2 to a cancer patient.

20. The use of a methylol transfer agent selected from taurolidine, taurultam, or a combination thereof, for reducing toxicity and side effects of IL-2 in the treatment of cancer in a cancer patient.

21. The use of claim 20 wherein said taurolidine, taurultam or combination thereof enhances efficacy of said IL-2.

22. The use of claim 20 wherein said taurolidine, taurultam or combination thereof is in an amount equivalent to about 0.1-1000 mg/kg patient body weight.

23. The use of claim 20 wherein said taurolidine is in an amount of about 10-20 mg.

24. The use of claim 20 wherein said taurolidine is at a dosage in an amount of about 250 ml 2% by weight taurolidine solution.

25. The use of claim 20 wherein said cancer is glioma, neuroblastoma, astrocytoma, carcinomatous meningitis, breast cancer, ovarian cancer, colon cancer, prostate cancer, pancreatic cancer, liver cancer, lung cancer, gastric cancer, esophageal

cancer, urinary bladder cancer, leukemia, lymphoma, melanoma, renal cell cancer or metastases thereof.

26. The use of claim 25 wherein said cancer is melanoma.

27. The use of claim 25 wherein said cancer is metastatic malignant melanoma.

28. The use of claim 25 wherein said cancer is metastatic renal cell carcinoma.

29. The use of claim 20 wherein said taurolidine, taurultam or a combination thereof is in an amount of 5 g.

30. The use of claim 20 wherein said taurolidine, taurultam or a combination thereof is in an amount of 10 g.