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(54) Titre : COMPOSITION PHARMACEUTIQUE POUR LE TRAITEMENT DU CARCINOME HEPATOCELLULAIRE
(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

(57) Abrégé/Abstract:
The invention mainly discloses a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, which comprises thalidomide and a pharmaceutically acceptable carrier.

ABSTRACT OF THE INVENTION

The invention mainly discloses a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, which comprises thalidomide and a pharmaceutically acceptable carrier.

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

BACKGROUND OF THE INVENTION

Thalidomide was first synthesized in 1953, and it was widely used as a sedative and for the prevention of vomiting during pregnancy. In 1963, it was found that women who took thalidomide in the first trimester of pregnancy would deliver terata, such as phocomelia. Therefore, thalidomide was prohibited in Europe and the USA.

In view of studies in recent years, thalidomide has the efficacy on adjustment of the immune system which may treat immune system related diseases. For instance, Arch Dermatol. 1993, vol. 129, p. 1548-1550 described the use of thalidomide in the treatment of cutaneous lupus erythematosus; the Journal of Rheumatology, 1989, 16, p. 159-163 described the use of thalidomide in the treatment of refractory rheumatoid arthritis; Arch Dermatol. 1990, vol. 126, p. 923-927 described the use of thalidomide in the treatment of Behcet's syndrome; Journal of Pediatr. Gastroenerol. Nurt. 1999, vol. 28, p. 214-216 described the use of thalidomide in the treatment of Crohn's disease; and Journal of Rheumatology, 1998, vol. 25, p. 964-969 described the use of thalidomide in the treatment of rheumatoid arthritis. In addition, US Patent Nos. 5,593,990 and 5,629,327 disclose that thalidomide could effectively inhibit angiogenesis; US Patent No. 5,654,312 discloses the methods of treatment for inflammatory and autoimmune dermatoses. In addition, the Journal of Infectious Diseases, 1993, 168, p. 408-414 taught that thalidomide could effectively inhibit tumor necrotic factor-alpha (TNF-I). Anti-Cancer Drugs, 1996, 7, p. 339-343 demonstrated that thalidomide could effectively inhibit basic fibroblast growth factor-induced angiogenesis. Thalidomide is widely applied in the clinical treatment of malignant tumors which are highly vascular and cannot be effectively treated by chemical therapy. For instance, US Patent No. 5,696,092 discloses the use of thalidomide in the inhibition of metastases of cancers of epithelial cell origin, especially human prostate cancers. Among the above prior art references, none of the references or patents teaches that thalidomide could be specifically used in the treatment of hepatocellular carcinoma.

Up to the present time, there are not any drugs that can effectively treat hepatocellular carcinoma. Patients with metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, normally survive for only three to four months. Metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, is mainly subjected to systemic therapy. The use of Doxorubicin, a high dosage of Tamoxifen in combination Doxorubicin or EA-PFL, is an effective example. The remission rate of those drugs can achieve levels between 15 and 30%. However, because the patients of hepatocellular carcinoma usually develop complication of liver cirrhosis and other complications (such as leukopenia, thrombopenia or liver function impairment), they cannot be subject to systemic chemotherapy.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows a computerized abdominal tomography of a patient, before and after, treatment with thalidomide. Fig. 1(a) and Fig. 1(b): before the treatment with thalidomide, the computerized abdominal tomography scan shows that the left and right hepatic lobes of the patient were infiltrated with diffused hepatocellular carcinoma. The depositing of Lipiodol™ on the liver lobes after arterial embolization is shown in Fig. 1(a) and Fig. 1(b). Fig. 1(b) also shows a 5 cm x 5 cm massive type index lesion at the left hepatic lobes. The concentration of alpha-fetoprotein in the patient's blood is 4335μg/ml. Fig. 1(c) and 1(d): after treatment with thalidomide, the computerized abdominal tomography scan shows that most diffused hepatocellular carcinoma, which infiltrated the left and right hepatic lobes of the patient, disappear. The massive type index lesion at the left hepatic lobe shown in Fig. 1(b) has been reduced to the size of 3 cm x 3 cm. The concentration of alpha-fetoprotein in the patient's blood is 1501 μg/ml. In addition, the scan show the occurrence of ascitic fluid. After the detection by abdominal paracentesis, it is proved that ascitic fluid was caused by spontaneous bacterial peritonitis. The existence of hepatocellular carcinoma was not shown.

Figure 2 shows the variation of the concentrations of alpha-fetoprotein in the patient's blood before and after the treatment with thalidomide.

SUMMARY OF THE INVENTION

An object of an aspect of the subject invention is to provide a pharmaceutical composition for use in the treatment of hepatocellular carcinoma.

Another object of an aspect of the subject invention is to provide a pharmaceutical composition for use in the treatment of metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, which comprises thalidomide and a pharmaceutically acceptable carrier.

Another object of an aspect of the subject invention is to provide a pharmaceutical composition used as adjuvant treatment for hepatocellular carcinoma, where local treatment has failed, such as percutaneous ethanol injection, operation, transcatheter arterial chemoembolization (TACE) or cryotherapy.

According to an aspect of the present invention, there is provided a pharmaceutical composition for use in treatment of hepatocellular carcinoma, consisting of 100 to less than 200 mg of thalidomide and a pharmaceutically acceptable carrier.

In accordance with another aspect of the present invention, there is provided a use of a dose of 100 to less than 200 mg of thalidomide for the treatment of hepatocellular carcinoma in a subject, where local treatment has failed.

In accordance with still another aspect of the present invention, there is provided a use of a dose of 100 to less than 200 mg of thalidomide in the manufacture of a medicament for the treatment of hepatocellular carcinoma in a subject, where local treatment has failed.

According to a further aspect, there is provided a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, consisting of a daily amount of 200 mg of thalidomide and a pharmaceutically acceptable carrier, wherein the composition is not for use in combination with ultrapheresis treatment.

According to another aspect, there is provided a use of a daily amount of 200 mg of thalidomide in the manufacture of a medicament for the treatment of hepatocellular carcinoma in a subject where local treatment has failed, wherein the subject was not subjected to ultrapheresis treatment.

According to a further aspect, there is provided a thalidomide, for use in the

treatment of hepatocellular carcinoma, consisting of a daily amount of 200 mg of thalidomide, wherein the thalidomide is not for use in combination with ultrapheresis treatment.

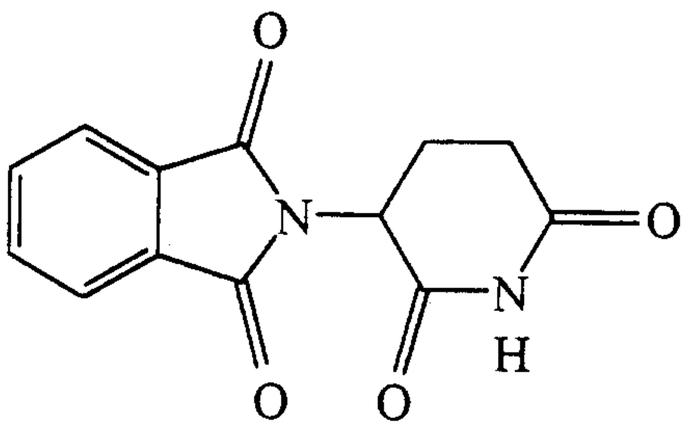
According to another aspect, there is provided a use of a daily amount of 200 mg of thalidomide for the treatment of hepatocellular carcinoma in a subject where local treatment has failed, wherein the subject was not subjected to ultrapheresis treatment.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention utilizes thalidomide to treat metastatic hepatocellular carcinoma and hepatocellular carcinoma, where local treatment has failed. Occasionally, the invention found that thalidomide has excellent effects concerning the treatment of such carcinoma which are difficult to treat. This includes the significant and rapid decrease of the concentration of alpha-fetoprotein, the reduction of tumors and the relief of symptoms for patients, without significant side effects, such as arrest of

bone mellow or hepatotoxicity.

The chemical nomenclature of thalidomide used in the subject invention is 2-(2,6-dioxo-3-piperidinyl)-1H-isoindolle-1,3(2H)-dione, which is a white crystal powder; odorless; mp 269-271 □C; sparingly soluble in water, methanol, ethanol or acetone. The chemical structure of thalidomide is as follows:



The term "pharmaceutically effective amount" used in the pharmaceutical composition of the subject invention is directed to the administered amount to mammals that need such treatment in order to proceed with the above-mentioned treatment. The pharmaceutically effective amount depends on the individual, the disease to be treated, the body weight and age of the individual, the level of the disease or the administration route. This can be determined by persons skilled in the art. The pharmaceutically effective amount of thalidomide used in the subject invention is usually 30 to 1200 mg, preferably 50 to 800 mg and more preferably 100 to 500 mg.

The pharmaceutical composition of the subject invention can be used in combination with other hepatocellular carcinoma treating drugs, such as anticancer chemotherapeutic drugs, hormones, biological response modifier(s), other angiogenesis inhibitors, immunological inhibition agents or gene therapeutic agents.

The pharmaceutical composition of the subject invention can be administered by different routes, comprising oral, rectal, topical subcutaneous, intravenous, intramuscular and nasal administration. The

compound is effective in both injective composition or oral composition form.

The therapeutic efficacy of the pharmaceutical composition of the subject invention comprising thalidomide on the treatment of hepatocellular carcinoma has been supported by clinical observation. An example is as follows:

A 44 year-old male patient with medical history of hepatitis C was diagnosed with hepatocellular carcinoma in December 1998 and treated with transcatheter arterial chemoembolization. He was treated with transcatheter arterial chemoembolization again in March and June 1999. According to the computerized abdominal tomography and gastrointestinal track barium enema, hepatocellular carcinoma invasion of the right colon and duodenum was doubted. The patient was treated with radiation on the right liver lobe during July to September 1999. After one-month of treatment, the concentration of alpha-fetoprotein in the patient's blood increased from 105μg/ml, before treatment, to 535 μg/ml. The follow-up magnetic resonance imaging (MRI) revealed that the hepatocellular carcinoma of the patient exacerbated and was complicated with tumor thrombosis of a portal vein. The patient was treated with a forth transcatheter arterial chemoembolization. The concentration of alpha-fetoprotein in the patient's blood was increased to 1572 μg/ml. In November 1999, the follow-up computerized abdominal tomography scan showed that the two hepatic lobes of the patient had wide hepatocellular carcinoma infiltration (as shown in Figs. 1(a) and 1(b)), esophageal and gastric varcose, tumor thrombosis of a portal vein and the main portal vain in the liver. The concentration of alpha-fetoprotein in the patient's blood was up to 4335 μg/ml. The liver function exacerbated that the total bilirubin was 9.2 mg%, GOT/GPT was 253/115 IU and alkaline phosphase (ALP) was 239 unit/l. As the liver function of the patient was significantly exacerbated, he was not suitable to take transcatheter arterial embolization therapy. 100 mg of Thalidomide was administered to the patient twice per

day. After two weeks of treatment, upper quadrant tenderness of the patient was significantly relieved. After four weeks, the concentration of alpha-fetoprotein in the patient's blood was decreased to 1501 μg/ml, total bilirubin was 10.2 mg%, GOT/GPT was 184/102 IU and alkaline phosphase was 233 unit/l. Meanwhile, the follow-up MRI showed that the hepatocellular carcinoma of the two liver lobes significantly remitted (as shown on left lower and right lower figures). However, ascitic fluid was found. The abdominal paracentesis evidenced that ascitic fluid was caused by spontaneous bacterial peritonitis. The existence of hepatocellular carcinoma was not shown. The patient was administered with antibiotics for the treatment of spontaneous bacterial peritonitis. The patient was still treated with thalidomide to the present. Figure 2 shows the variation in the concentrations of alpha-fetoprotein in the patient's blood. After treatment with thalidomide, the concentration of alpha-fetoprotein significantly decreases.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of hepatocellular carcinoma, consisting of a daily amount of 200 mg of thalidomide and a pharmaceutically acceptable carrier, wherein the composition is not for use in combination with ultrapheresis treatment.

2. The pharmaceutical composition according to claim 1 for use in the treatment of hepatocellular carcinoma, where local treatment has failed.

3. The pharmaceutical composition according to claim 1 for use as an adjuvant treating agent in the treatment of hepatocellular carcinoma.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein said daily amount is divided for use twice daily.

5. Use of a daily amount of 200 mg of thalidomide in the manufacture of a medicament for the treatment of hepatocellular carcinoma in a subject where local treatment has failed, wherein the subject was not subjected to ultrapheresis treatment.

6. The use according to claim 5, wherein said daily amount is divided for use twice daily.

7. Use of a daily amount of 200 mg of thalidomide for the treatment of hepatocellular carcinoma in a subject where local treatment has failed, wherein the subject was not subjected to ultrapheresis treatment.

8. The use according to claim 7, wherein said daily amount is divided for use twice daily.

9. Thalidomide, for use in the treatment of hepatocellular carcinoma, consisting of a daily amount of 200 mg of thalidomide, wherein the thalidomide is not for use in combination with ultrapheresis treatment.

10. The thalidomide according to claim 9 for use in the treatment of hepatocellular carcinoma, where local treatment has failed.

11. The thalidomide according to claim 9 for use as an adjuvant treating agent in the treatment of hepatocellular carcinoma.

12. The thalidomide according to any one of claims 9 to 11, wherein said daily amount is divided for use twice daily.

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UNSCANNABLE ITEM

RECEIVED WITH THIS APPLICATION

(ITEM ON THE 10TH FLOOR ZONE 5 IN THE FILE PREPARATION SECTION)

DOCUMENT REÇU AVEC CETTE DEMANDE

NE POUVANT ÊTRE BALAYÉ

(DOCUMENT AU 10 IÈME ÉTAGE AIRE 5 DANS LA SECTION DE LA

PRÉPARATION DES DOSSIERS)

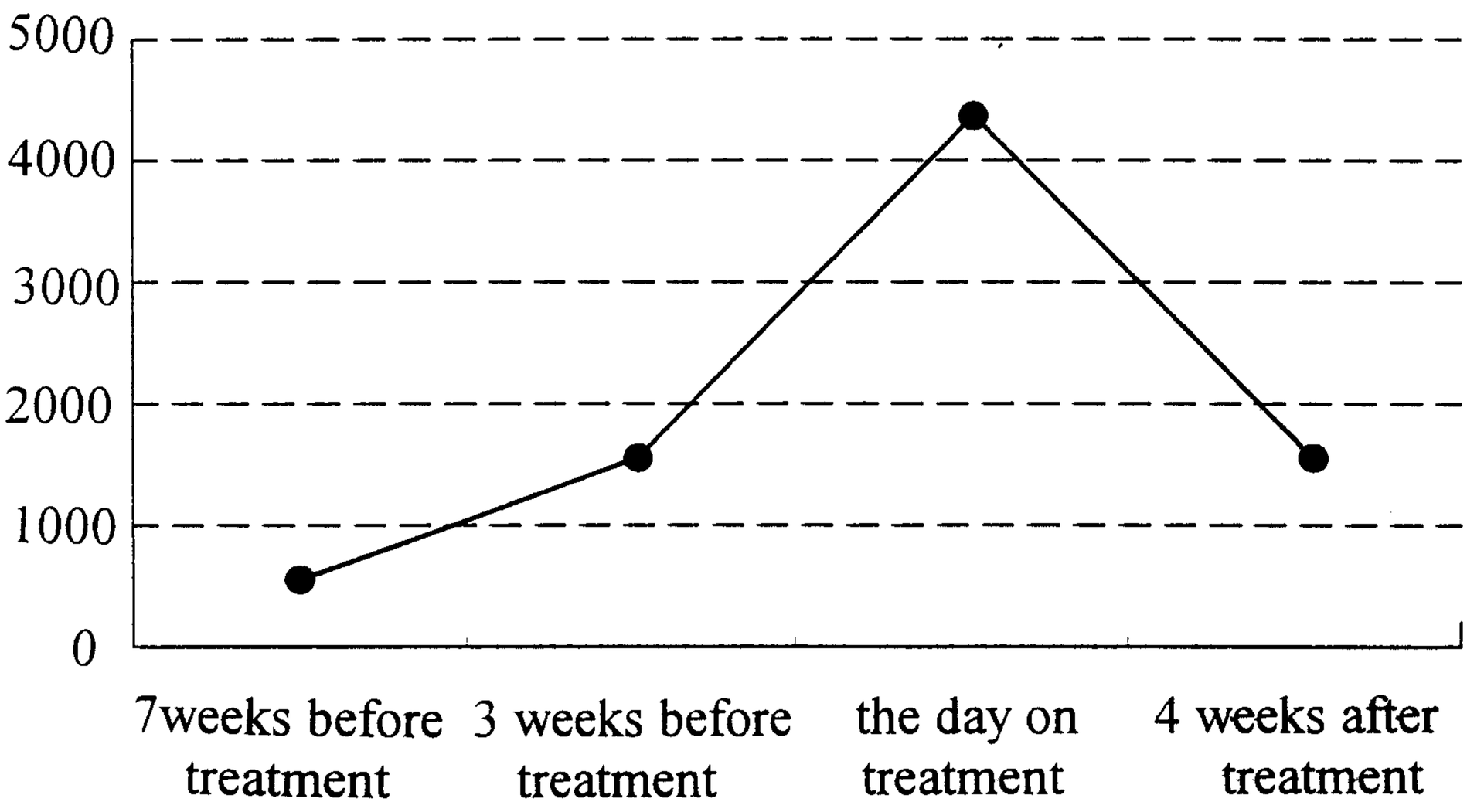

5000
4000
3000
2000
1000
0
7weeks before treatment
3 weeks before treatment
the day on treatment
4 weeks after treatment

FIG.2