Hexadecylphosphocholine (D 18506) in the Topical Treatment of Skin Metastases: A Phase-I Trial

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Introduction

Skin metastases often present a severe problem in medical oncology predominantly in patients refractory to radiation or chemotherapy. Topical application of anticancer agents might be a way to treat metastases of the skin and to control local tumor growth without major systemic toxicity [1]. Hexadecylphosphocholine (HePC, D18506), a representative of a new class of antineoplastic agents developed in our laboratory [2], was selected because of its superior antitumoral activity on chemically induced autochthonous rat mammary carcinoma [3, 4]. The compound was dissolved in short chain 1-0-alkylglycerols because the glycerol derivatives have been shown to enhance permeation of drugs through biological membranes [5], suggesting an easier penetration of HePC into the skin.

Patients and Methods

HePC was prepared according to the general procedures for the conversion of alcohols to the respective phosphocholines as described by Eibl [6]; 1-0-alkylglycerols were synthesized as described elsewhere [7]. Later, these compounds were synthesized by ASTA Pharma AG (Bielefeld, FRG).

For topical application, HePC was dissolved in a mixture of short chain 1-0-alkylglycerols and water. For this purpose, 1-0-propylglycerol, 1-0-hexylglycerol, 1-0-nonylglycerol and water were mixed in a ration of 2/1/1/2 on a weight basis. The final concentrations of HePC in the solution was 20, 40, 60 and 80 mg/ml, respectively. The resulting formulation, called KASKADE for short, is slightly viscous and could be applied to the skin without problem. Twenty-five patients with metastatic breast cancer and progressive skin metastases were entered into the clinical trial, 24 of which were evaluable. All 24 patients were extensively pretreated. 22 patients had surgery, 18 patients had radio-, chemo- and hormone therapy, 2 had radio- and

chemotherapy, 3 had radiotherapy and hormones and 1 had radiotherapy only. No other antiproliferative treatment was administered 3 weeks before and during topical HePC therapy. The study protocol was reviewed and approved by the ethical board of the University of Göttingen. After written consent, KASKADE was applied once a day for 5 days. In the case of proven local tolerance, the substance was applied twice daily until a complete remission or progressive disease was observed. In order to detect systemic side effects blood and urine analyses, ECG and radiographic controls were performed.

Results

Within the framework of the clinical phase-I trial, local recurrence on the skin in patients with metastatic breast cancer were treated topically. To test the local tolerance of the KASKADE, the concentrations of HePC in the mixture were progressively increased from 20 mg up to 80 mg/ml in the same patient. All 24 patients received 20 mg HePC/ml. In 13 patient, the dose was escalated to 40 mg/ml, in 11 patients to 60 mg/ml and in 5 patients 80 mg HePC/ml. The local tolerance of the mixture was good. Local side effects were reddening, dryness of the skin, epithelial scaling and, in individual cases, itching. In particular, it should be stressed that neither hematotoxic nor other blood chemistry changes could be observed. We noted 3 complete remissions (1–6 months), 3 partial remissions (2–12 months), 6 no changes (2–12 months) and 12 progressive diseases. The 3 patients with a complete remission had few to multiple flat skin metastases up to a maximal diameter of 2 cm. One of these patients responded to 20 mg, the other 2 at a dose level of 40 mg HePC/ml.

A partial response lasting 12 months to date could be observed in a patient with multiple flat skin metastases in the margin of a skin graft. Radiation of the involved area was without visible effect. Four weeks after starting topical therapy, a partial remission was detectable which is still ongoing at a dose level of 60 mg HePC/ml.

Skin biopsies from 2 patients after 3 months of topical treatment revealed normal skin architecture. However, a slight to modest increase in collagen content compared to untreated skin specimens could be observed. In another patient with a markedly exulcerated local recurrence, topical therapy had been initiated 5 weeks before death. Postmortem biopsies revealed epithelial proliferation in the tumor periphery as well as heavily damaged tumor cell clusters.

Discussion

The topical application of anticancer drugs represents a new approach in cancer therapy. Among the various drugs, alkyl-phosphocholines seem to be very suitable for topical application because of their favorable affinity to biological membranes. This property results in good penetration characteristics,

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prerequisite to effective treatment of dermatological tumors and metastases. Moreover, the short chain 1–0-alkylglycerols used in the KASKADE formula have antiproliferative activity of their own on different tumor cells in vitro. Depending on the length of the alkyl chains, bacteriocidal and fungicidal properties have been noted which might be of advantage in cases of infected skin areas. The results of the topical treatment on breast cancer patients are promising. Although this approach is most likely to be limited to palliative treatment regimens, it seems to be a therapeutic alternative in heavily pretreated patients. This is strikingly supported by the absence of any systemic side effects and the good local tolerance of the KASKADE even in long-term application. An even greater advantage to this therapy is that the patients can apply the

KASKADE themselves. Based on these hopeful results, a multicentric phase-II study has just been initiated.

References

1 Unger, C; Eibl, H.; Heyden, H.W. von; Nagel, G. A.: Etherlipids in the topical treatment of skin metastases. Proc. Am. Ass. Cancer Res. 29: 357 (1988).

Eibl, H.; Unger, C: Phospholipide als Antitumormittel: Möglichkeiten einer selektiven Therapie; in Aktuelle Onkologie, vol. 34, pp. 1–18 (Zuckschwerdt, München 1987).

Muschiol, C; Berger, M.R.; Shuler, B.; Scherf, H.R.; Garzon, F.T.; Zeller, W.J.; Unger, C; Eibl, H.; Schmähel, D.: Alkylphosphocholines: Toxicity and anticancer properties. Lipids 22: 930–934 (1987).

Hilgard, P.; Stekar, J.; Voegeli, R.; Engel, J.; Schuhmacher, W.; Eibl, H.; Unger, C; Berger, M.: Characterization of the antitumor activity of hexadecylphosphocholine (D 18506). Eur. J. Cancer clin. Oncol. 24: 1457–1467 (1988).

Unger, C; Eibl, H.; Heyden, H.W. von; Krisch, B.; Nagel, G.A.: Blut-Hirnschranke und Penetration von Zytostatika. Klin. Wschr. 63: 563–571 (1985).

Eibl, H.; Wooley, P.: A general synthetic method for enantiomerically pure ester and ether lysophospholipids. Chem. Phys. Lipids 47: 63–68 (1988).

Unger, C; Eibl, H.; Heyden, H.W. von; Nagel, G.A.: Ein neues Prinzip zur Überwindung der Blut-Hirn-Schranke; in Aktuelle Onkologie, vol. 13, pp. 31–38 (Zuckschwerdt, München 1984).

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