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A Cholesterol Derivative (Hydroxysterol; 24-Ethyl-Cholestane-3 β ,5 α ,6 α -Triol) With High Antitumor Activity Against a Variety of Sarcomas

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Abstract

Oxygenated derivatives of cholesterol, Oxysterol, have different physicochemical properties acting on cell membranes. Agents belonging to this class of compounds have been found to induce apoptosis and to harbour antitumor activity demonstrated in vitro and in vivo. 24-ethyl-cholestane- 3β, 5α, and 6α-triol is a new hydroxysterol developed in our lab. Unlike other derivatives, it is, to our knowledge, the first one tested in the clinic. We have treated eight patients suffering from different types of sarcomas with bad performance status. Three patients were suffering from carcinosarcomas, one from angiosarcoma, one from osteosarcoma, one from low-grade chondrosarcoma, one from poorly differentiated sarcoma and one from Ewing sarcoma. All of them were pre-treated with chemotherapy with or without radiotherapy. Seven patients were females and one male with ages ranging from 21 to 82 (median age 55 y). None of these 8 patients experienced any side-effect despite the fact that one of them was taking a mild chemotherapy in association with hydroxysterol. This patient was excluded from the evaluation of the response to therapy. Among the 7 patients evaluable for response, we observed 4 complete responses (one of them confirmed by PET scan), two stable diseases and one progressive disease. The complete responses were observed in one osteosarcoma, one Ewing sarcoma, one angiosarcoma and one carcinosarcoma. As with our previous experience with this drug, no clinical or biological side-effect was observed and symptom control was achieved rapidly in all 6 symptomatic patients. We believe that this new compound deserves to be tested in phase II trials in patients suffering from sarcomas.

Keyword: Oxysterol; Hydroxysterol; 24-Ethyl-Cholestane-3β, 5α, and 6α-Triol; Carcinoma; Sarcoma; Carcinosarcoma

Introduction

Oxysterol are oxygenated derivatives of cholesterol. They have nuclear receptors and have been shown to pass cell membranes and the blood-brain barrier at a faster rate than cholesterol itself. In addition, Oxysterol have been ascribed a number of important roles in connection with cholesterol turnover, atherosclerosis, apoptosis, and necrosis [1-4]. Oxysterol have been shown to have antitumor effects on experimental models. These compounds however may be toxic and to our knowledge, although some derivatives have been tested in animals [5-10], none have reached the clinical level. 24-ethyl-cholestane- 3β, 5α, 6α-triol is a new Hydroxysterol developed in our lab. (US patent: Pct/us 2006/045665). An oral form of this compound has been tested in mice and rats and has shown neither acute nor chronic toxicity. It has also been tested on animal tumor models and on human cancer xenografts. The results of these tests were very promising showing an anti-tumor activity on a panel of tumor cell lines (data on file). Our experiments on humans have shown no toxicity for this drug. We have treated many patients with a variety of solid tumors with encouraging results [11].

Material and Method

From June 2007 to October 2009, we have treated a series of eight successive patients suffering from different types of sarcomas on a compassionate basis, because we did not have any on-going trial in sarcomas. Furthermore, most of these patients would not have been eligible for a clinical trial because of their bad performance-status. Seven patients were females and one male with ages ranging from 21 to 82 (median age 55 y). Three patients were suffering from carcinosarcomas, one from angiosarcoma, one from osteosarcoma, one from low-grade chondrosarcoma, one from poorly differentiated sarcoma and one from Ewing sarcoma. All of them were pre-treated with chemotherapy with or without radiotherapy (Table 1). We present in this article the retrospective analysis of this series.

24-ethyl-cholestane- 3β, 5α, 6α-triol was used as an oral formulation containing 100 mg of drug per pill. Since this drug was proven to be non-toxic on animals and on humans, the dose used in this series was guided by previous experiments with various doses at which antitumor activities were observed. This dose was fixed at 450 mg/sqm BID; (approximately 4 pills BID) continuously. Adverse events were reported according to the NCI- CTC classification and response evaluation was

Patient	Age	Type of Sarcoma	Previous Treatments (Number of Chemotherapy Regimens)	Response
1	58	Poorly Diff. Sarcoma	Chemotherapy (2)+ Radiotherapy	NC
2	22	Low-grade Chondrosarcoma	Chemotherapy(2)+ Radiotherapy	NC
3	70	Carcinosarcoma	Chemotherapy(2)	CR
4	22	Ewing Sarcoma	Chemotherapy(3)+ Radiotherapy	CR
5	59	Carcinosarcoma	Chemotherapy(2)+ Radiotherapy	PR(+chemo)
6	52	Carcinosarcoma	Chemotherapy(1)+ Radiotherapy	PD
7	21	Osteosarcoma	Chemotherapy(3)+ Radiotherapy	CR
8	82	Angiosarcoma	Chemotherapy(2)+ Radiotherapy	CR

Table 1: Summary of Patients Characteristics and Response.

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assessed according to recist criteria. All patients included in this study have given their informed written consent and the study protocol was approved by an appropriate ethics committee.

Result

None of these 8 patients treated with 24-ethyl-cholestane- 3β, 5α, 6α-triol experienced any clinical or biological side-effect despite the fact that one of them was taking a mild chemotherapy in association with hydroxysterol. This patient was excluded from the evaluation of the response to therapy. Among the 7 patients evaluable for response, we observed 4 complete responses (one of them confirmed by PET scan). Two had a stable disease and one a progressive disease. The complete responses were observed in one osteosarcoma, one Ewing sarcoma, one angiosarcoma and one carcinosarcoma (Figure 1a and 1b).

Shows a frontal view of a PET scan performed in one patient with Ewing Sarcoma with a huge right axillary metastasis (Figure 1b). Shows a complete clearance of this metastasis after treatment with hydroxysterol (Figure 2a and 2b).

Show a transversal view of this same PET scan, respectively before and after therapy observed 2 months after therapy. (Figure 3) shows a CT image of an angiosarcoma of the lung before treatment and (Figure 4) shows a complete clearance after treatment. The patient with a spinal chondrosarcoma had one localization at the cervical level previously treated with surgery and radiotherapy and localization at the dorsal level. This latter localization was completely cured with 24-ethyl-cholestane- 3β, 5α, 6α-triol.

Six of the eight patients were under pain killers when they started their treatment with 24-ethyl-cholestane- 3β, 5α, and 6α-triol. Two of them were taking mild opioids and 3 other patients were under morphine. Most of these patients had a rapid pain control within a few days after start of therapy with hydroxysterol. All of them stopped taking pain killers except one patient who was under morphine and finished up with mild anti-inflammatory drugs.

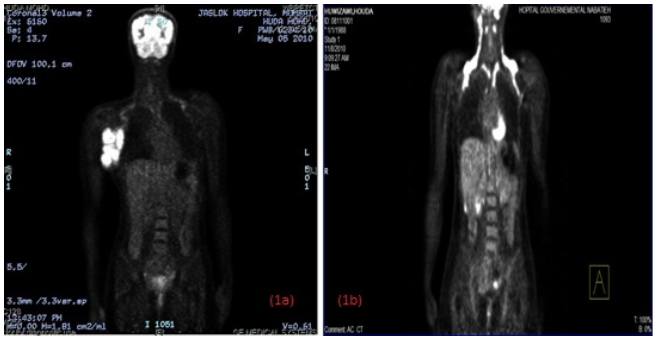

Figure 1: Ewing sarcoma. PET scan frontal view (a: before treatment, b: after treatment).

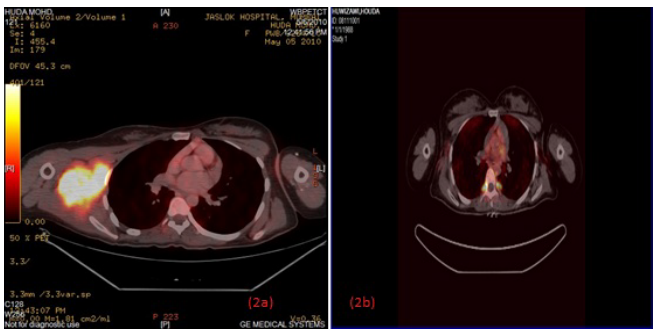

Figure 2: PET scan Transversal section (a: before treatment, b: after treatment).

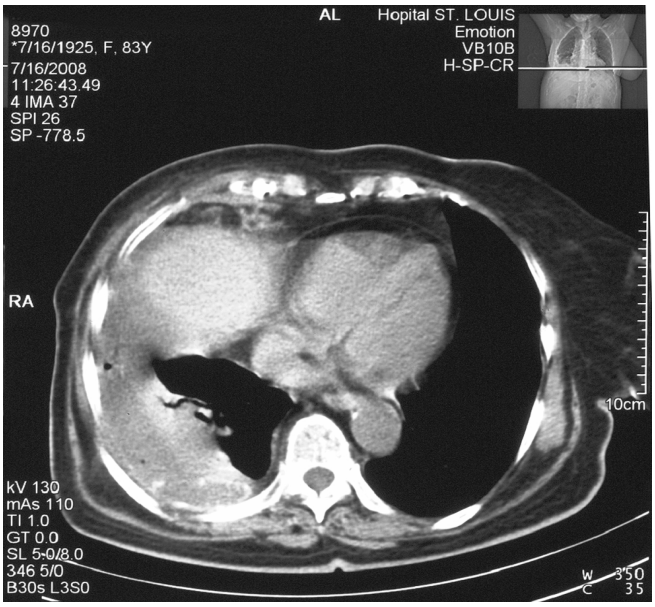

Figure 3: CT scan of an angiosarcoma of the lung before treatment.

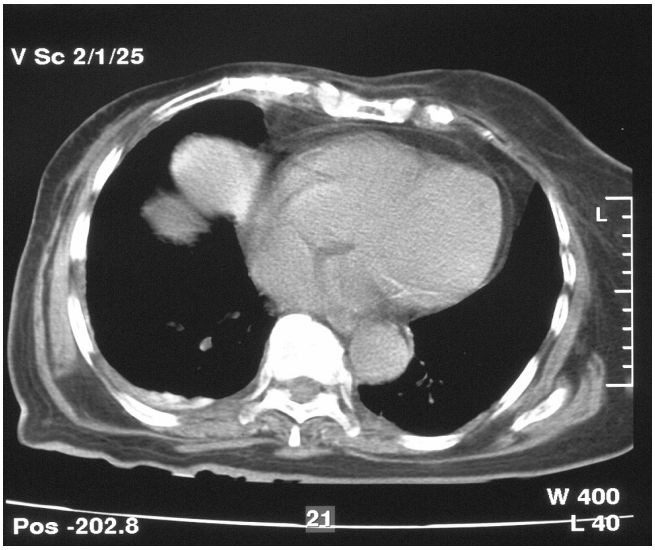

Figure 4: CT scan of an angiosarcoma of the lung after treatment.

Discussion

This is a retrospective analysis of a series of 8 successive heavily pre-treated patients suffering from various types of advanced sarcomas treated in our institution with 24-ethyl-cholestane- 3β, 5α, and 6α-triol. These patients had poor performance status and six of them suffered from severe pain. We observed in all symptomatic patients a rapid and dramatic improvement in their quality of life and a rapid pain control. The high rate of clinical benefit achieved along with a relative high