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Research Article

A Phase II Trial in Advanced and Metastatic Breast Cancer with a Cholesterol Derivative (Hydroxysterol; 24-Ethyl-Cholestane-3β,5α,6α-Triol) Showing High Activity and No Toxicity

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Abstract

Breast cancer is the deadliest form of cancer in women worldwide and all current therapies are associated with side effects which may on some occasions be severe without major impact on survival. Oxysterols are oxygenated derivatives of cholesterol. Oxysterols participate in the regulation of cholesterol metabolism, enzyme activity, and signaling pathways such as Hedgehog, Wnt, and MAPK. Some of these derivatives have been found as pro-inflammatory factors to promote human cancers while others have been found in experimental models to have an anti-proliferative effect. Most of these compounds have been shown to be very toxic. Our new drug (24-ethyl-cholestane-3β,5α,6α-triol) is the first oxysterol to have reached the clinical level and it has been shown to be very safe. Preliminary results in a variety of tumors have been very encouraging. We performed a phase II trial with patients suffering from advanced and metastatic breast cancer using this new compound. Thirty-four patients were included in this study. The median age was 55 years. Thirty-one patients had stage IV and three stage III. All had received at least one line of chemotherapy (some received more than 4 lines of therapy) and all except 3, previous radiotherapy. Twenty patients had a PS:1, nine had a PS:2 and five had a PS:3. Eighty percent were symptomatic and sixty-five percent were taking painkillers. Patients received daily 10 mg/Kg of oral (24-ethyl-cholestane-3β,5α,6α-triol) divided into 3 equal doses, until disease progression. Two patients exhibited a complete remission (CR). Twenty-one patients had a partial response (65%), Six patients had a stable disease/no change (SD/NC) and five patients had a disease progression (PD). The median duration of response was 9 months and 4 patients are still under treatment. One patient with leptomeningeal involvement is still alive and under treatment after 49 months. One patient was suffering from an intramedullary metastasis which was completely cleared off. No toxicity was observed so ever. Eighty percent of symptomatic patients had a remarkable symptom control. These encouraging results make this new and safe drug a good candidate for further clinical trials either alone or in association with other drugs in advanced breast cancer.

Keywords: Hydroxysterol; 24-ethyl-cholestane-3β,5α,6α-triol; Carcinoma; Advanced; Metastatic breast cancer; New drugs

Introduction

Breast cancer remains the most frequent and the deadliest type of cancer in women. Patients with advanced disease have a dismal prognosis and only 25% of patients according to the NCI remain alive at 5 years. All known treatments i.e Chemotherapy, hormonal drugs, biological and targeted therapies are all associated with side effects (sometimes severe) and have a very little beneficial effect on survival. Oxysterols are oxygenated derivatives of cholesterol. They have been shown to interfere

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with proliferation and cause the death of many cancer cell types, such as leukemia, glioblastoma, colon, breast, and prostate cancer cells. They control the transcription and the turnover of the key enzyme in cholesterol synthesis. Oxysterols interfere with ERK, hedgehog and want pathways of proliferation and differentiation. When administered in vitro to cancer cell lines, oxysterols invariably both slow down proliferation and provoke cell death [1-4]. Many of these compounds show antitumor activity in experimental models and most of them are very toxic [5-10]. (24-ethyl-cholestane-3β,5α,6α-triol) is a new oxysterol developed in our laboratory (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. Our experiments on humans have shown no toxicity for this drug and preliminary results were very encouraging in a variety of solid tumors and even in refractory tumors such as sarcomas [11-13]. We describe in this article the results of a phase II trial performed in patients suffering from advanced and metastatic breast cancer.

Material and Methods

From April 2013 to August 2017, we have treated a series of 34 patients suffering from advanced and metastatic breast cancer. Since we knew from previous studies that our drug does not have any side effect, the only exclusion criteria for the eligibility in this trial was a life expectancy less than 2 months and patients unable for medical reason to take oral drugs. As shown in Table 1, the median age was 55 years (range: 21-82). All patients were pretreated with chemotherapy and most often with hormonal treatments with or without radiotherapy. Thirty-one patients had stage IV and three stage III.

Table 1: Patients characteristics of the patients.

Number of Patients (Total 34)	
Age (years old)	**55 range (21-82)**
Ductal CA	28
Lobular CA	6
Previous Chemo 1 regimen	18
Previous Chemo 2 regimen	10
Previous Chemo 3 or more regimen	6
Previous Hormono 1 Regimen	14
Previous Hormono 2 or more regimen	12
Previous Radiotherapy	29

All had received at least one line of chemotherapy (some received more than 4 lines of therapy) and all except 3 received the previous radiotherapy. Twenty patients had a PS:1, nine had a PS:2 and five had a PS:3. Eighty percent were symptomatic and sixty-five percent were taking painkillers. This article summarizes the results of this phase II trial. (24-ethyl-cholestane-3β,5α,6α-triol) was administered in an oral form containing 100 mg of active compound per pill. Previous experiments on animals and humans had previously demonstrated the safety of this new drug and the dose selected for this study was guided by previous experiments with variable doses at which antitumor activities were observed. The patients were administered 450 mg/sqm BID; (approximately 4 pills BID) continuously until disease progression. The Recist criteria were used to evaluate the response to treatment and the toxicities were reported according to the NCI-CTC classification. Informed consent was signed by the patients prior to their inclusion in this study.

Results

We observed as shown in Table 2 about two complete responses. Twenty-one patients had a partial response (65%), Six patients had stable disease (NC) and five patients had a disease progression (PD). Overall 29 patients (85%) had a clinical benefit.

Table 2: Response to treatment, CR: complete response PR: partial response NC: no change/stable disease PG: progressive disease clinical benefit=CR+PR+NC.

Response	**Number** (%)	**Median duration of response**
CR	2	
PR	21 (65%)	9 months (2-49)
NC	6	
PG	5	
Clinical benefit	29 (85%)	

The median duration of response was 9 months and 4 patients are still under treatment. One patient with leptomeningeal involvement is still alive and under treatment after 49 months. One patient was suffering from an intramedullary metastasis which was completely cleared off. All sites of metastases were responsive to treatment. Figure 1 shows the bone scan of a patient with bone metastasis with a clear improvement after 4 months of treatment. Figure 2 shows a complete response of a brain metastasis on MRI. Figure 3 (a,b) shows an almost complete response on PET scan of liver and bone metastases after 6 months of therapy. In another patient as shown in Figure 4 (a,b) massive liver metastases were cleared off after 7 months of treatment. Figure 5 (a,b) shows the clearance of lung metastases. None of the 34 patients treated with 24-ethyl-cholestane-3β,5α,6α-triol experienced any clinical or biological side-effect. We observed in eighty percent of symptomatic patients a remarkable symptom control with a rapid and dramatic improvement in their quality of life.

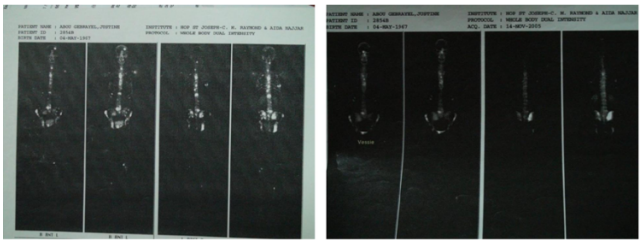

Figure 1: Bone scan of a patient with bone metastasis before therapy and after post therapy.

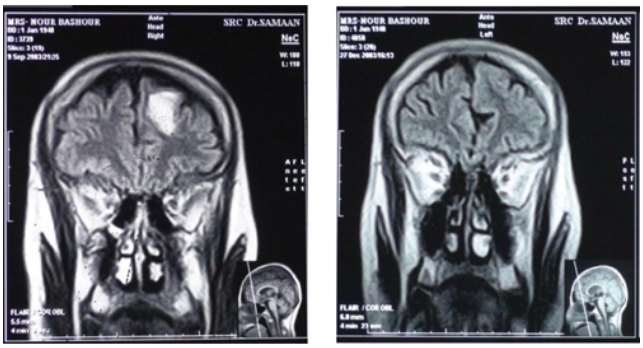

Figure 2: Brain Metastases before treatment and after treatment on MRI.

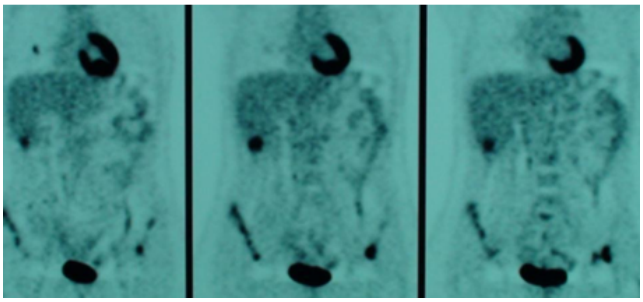

Figure 3(a): Bone and liver metastases on PET scan before treatment.

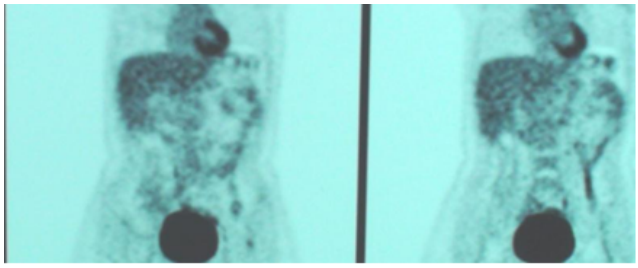

Figure 3(b): Bone and liver metastases on PET scan after 6 months of treatment.

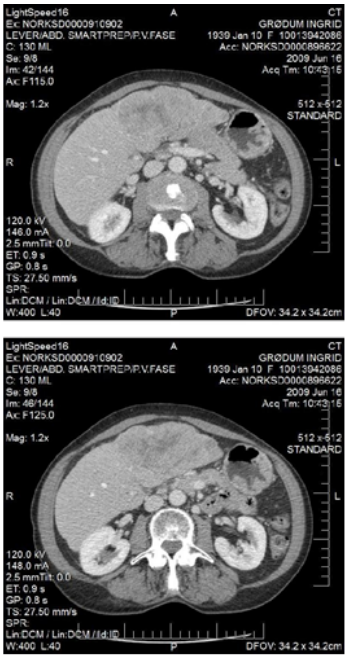

Figure 4(a): Massive liver metastases on CT scan abdominal CT scan at the beginning of treatment.

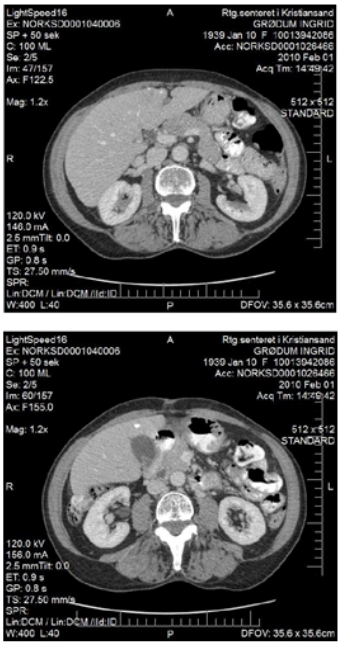

Figure 4(b): Massive liver metastases on CT scan abdominal CT scan after 7 months of treatment.

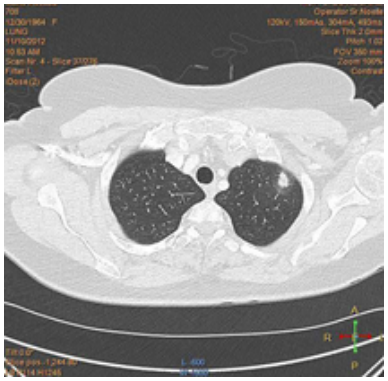

Figure 5(a): Lung metastases on CT scan before treatment.

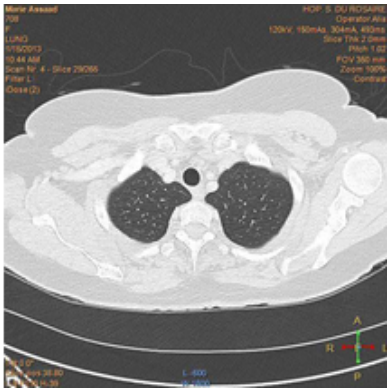

Figure 5(b): Lung metastases on CT scan after 2 months treatment.

Discussion

This is a prospective phase II trial evaluating the efficacy of a new drug which is the (24-ethyl-cholestane-3β,5α,6α-triol) in advanced and metastatic breast cancer. This drug is the first of its class (oxysterols) to be safe enough to be tested in the clinic. None of 34 patients in this study suffered from any side-effect. Eighty-five percent of these heavily pretreated patients experienced a clinical benefit and most of the symptomatic patients had a rapid pain control and an improvement in their quality-of-life. There are no, to our knowledge, in the anti-cancer armamentarium, drugs totally safe which can achieve such results. We believe that with this exciting performance this new and safe drug is a good candidate for further clinical trials either alone or in association with other drugs in advanced breast cancer.

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