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Original article

A phase 1/2 of a combination of Cetuximab and Taxane for "triple negative" breast cancer patients

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ABSTRACT

50–70% of tumors of the so called "triple negative" subtype of breast cancer express EGFR. We hypothesized that addition of anti EGFR to Taxanes will result in increased effectiveness in EGFR expressing tumors. Here we set out to obtain data regarding the safety, tolerability and also the effectivity of the combination of weekly Taxane treatments with Cetuximab -an anti EGFR antibody in this subgroup of breast cancer. 18 triple negative breast cancer patients were treated with weekly Cetuximab and Taxane therapy. Addition of Cetuximab resulted in controllable Dermatologic toxicity in most patients –with grade 3 in two patients. Some impressive results were noted including one CR, one near CR and regression of chemotherapy and radiation resistance skin metastasis. Median TTF -and overall survival –6 and 12 months. Administration of Taxane Cetuximab weekly therapy for triple negative breast cancer patients is feasible. Use of anti EGFR-Taxane combinations should be assessed in larger clinical trials in this patient population perhaps in a similar manner to the lung cancer patients only in those with strong EGFR expression.

Introduction

Triple negative breast cancer is defined by the lack of expression of three receptors Estrogen Receptor, Progestron Receptor and HER2 [1,2]. It accounts for around 15% of all breast cancers. Disease course is more aggressive than other breast cancer subtypes [3].

Tumors of this subtypes are unresponsive to hormonal or anti HER2 agents. Thus there is a need to define new chemotherapeutic–biologic combinations which will be active in this breast cancer subtype.

Epidermal Growth Factor Receptor (EGFR also known as HER1) has been shown to be overexpressed in a substantial percentage of triple negative breast cancers [4]. EGFR is part of the human epidermal growth factor receptor family and can form heterodimers with HER2 and other Her family members. It activates a similar signal transduction pathway to HER2 [5]. Taxanes are among the most active anti breast cancer agents. In tissue culture this agents have demonstrated additive and even synergistic activity together with an anti HER2 antibody [6–8]. EGFR has been shown to be overexpressed in a substantial percentage of triple negative breast cancer tumors. Interestingly some TNBC cell lines overexpressing the receptor are growth inhibited by the anti-EGFR monoclonal antibodies [9]. We hypothesized that similar to the activity of Taxane anti HER2 combination in HER2 overexpressing tumors, Taxanes anti EGFR(HER1) antibodies combination would be active in some triple negative breast cancers.

In colon cancer where percentages of EGFR expressing tumors are high responses to anti EGFR therapy was found to be independent EGFR expression. Similarly in triple negative breast cancer there is a substantial fraction of tumors expressing EGFR [4]. We therefore recruited to our clinical study patients regardless of the tumor expression levels of EGFR.

Here we describe a clinical trial using the combination of weekly Taxane therapy with the chimeric anti human EGFR antibody Cetuximab.

Our most important goal was to study tolerability to this combination in this group of patients and obtain initial data as to response to treatment. We have also followed tumor responses, progression free survival and survival of all the treated patients.

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Table 1a
Patients characteristics, previous chemotherapies.

Chemotherapy	*N* (%)
CAF + paclitaxel	6 (33.3)
CAF	3 (16.7)
Adriamycin	2 (11.1)
Adriamycin + capcetabine	1 (5.6)
Adriamycin + paclitaxel	1 (5.6)
CAF + paclitaxel + herceptin	1 (5.6)
CAF + carboplatin	1 (5.6)
CAF + paclitaxel + eribulin	1 (5.6)
CMF	1 (5.6)

CAF, cyclophosphamide, doxorubicin, fluorouracil; CMF, cyclophosphamide, methotrexate, fluorouracil.

Table 1b
Patients characteristics, EGFR staining results.

EGFR staining		*N*
EGFR staining	*N* (%)	
+1	3 (30)	
+2	1 (10)	
+3	6 (60)	
EGFR staining		(10)

Preliminary results of our study have been presented in the ASCO meeting 2009.

Methods

Patients with metastatic breast cancer with a tumor phenotype similar to that of the basal-like carcinomas (namely high-grade tumors negative for HER2, ER and PR) with an *Eastern Cooperative Oncology Group* (ECOG) performance status up to 2, and up to two previous chemotherapy treatment lines in the metastatic setting could be recruited to the trial. Patients were recruited even without measurable tumor with bone disease only and also following previous Taxane treatments at the adjuvant settings. Exclusion criteria included – the presence of concurrent active second cancer, Brain metastasis, liver enzymes or Creatinine X3 of upper limit of normal.

Agents

Cetuximab: an initial loading dose of cetuximab 400 mg/m^2 (200 mL/m^2) was administered over a period of 120 min (maximum infusion rate of 5 mL/min). The initial dose of cetuximab was followed by a weekly dose of 250 mg/m^2 (125 mL/m^2) administered over a period of 60 min (maximum infusion rate of 5 mL/min).
Paclitaxel 80 mg/m^2 was administered weekly, while in two patients suffering from peripheral therapy due to previous studies we used weekly **Docetaxel** at an initial dose of 30 mg/m^2.

The protocol was approved the Hadassah Medical Center ethics committee and the study was carried out in accordance with the Declaration of Helsinki.

Response assessment

We assessed treatment responses by

- Objective tumor response- as measured by CT scans according to Recist version1.0.
- Tumor marker response for patients with high levels of CA15-3 or CA125 if it was unrelated to pleural or peritoneal fluids.
- Clinical response-as assessed by the treating physician – every 6–10 weeks
- Time to treatment failure.

Statistical analysis

As this was a small study and multivariate analysis was therefore limited, the results are mainly descriptive. Kaplan Meyer survival and Time to treatment failure were calculated utilizing the

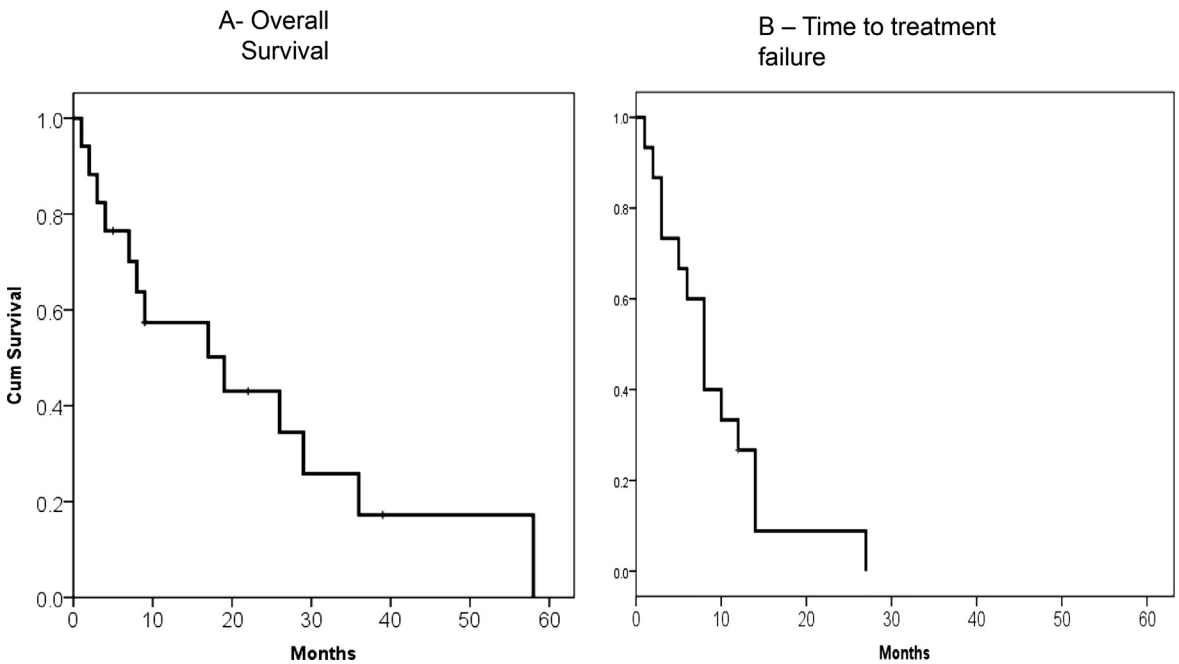

Fig. 1. Left – Time to treatment failure – median time was around 6 months. A Kaplan Meyer curve. Figure 1-right –Survival times. A Kaplan Meyer curve – only one patient is currently alive. Median survival is around 12 months.

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