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Report

Phase II evaluation of interferon added to tamoxifen in the treatment of metastatic breast cancer

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Abstract

This phase II trial evaluated the clinical role of interferon (IFN) in overcoming tamoxifen (TAM) resistance in breast cancer. Twenty women and 1 man received recombinant alpha interferon (5 million units per meter squared intramuscularly, 5 times per week) plus TAM (10 mg orally, twice daily) for the treatment of metastatic breast cancer, either after failing tamoxifen therapy or as frontline hormonal therapy.

Of the 9 evaluable patients with disease progression after an objective response to TAM, there were no partial or complete responses with the addition of IFN. Ten evaluable patients received TAM plus IFN as frontline hormonal therapy with 2 complete and 3 partial responses for an overall response rate (RR) of 50% (95% confidence interval = 19–81), a 71% RR for ER-positive patients (95% confidence interval = 29–96) and no responses in ER-unknown patients.

Sixteen patients required dose reductions of IFN and 8 patients discontinued therapy due to toxicity.

It is unlikely that the RR for TAM plus IFN is greater that than seen with TAM alone, or that the addition of IFN to TAM therapy can overcome clinical TAM resistance.

Endocrine therapy plays an important role in the management of breast cancer [1]. Approximately 30% of unselected patients and 50 to 60% of patients with estrogen receptor (ER) positive tumors will respond to hormonal manipulations [2]. In addition, response rates are proportional to the level of ER [2], and resistance is often associated with a loss of the ER [3, 4]. This suggests that the presence of a functioning ER is important for the action of antiestrogen drugs and up-regulation of the ER may retard or reverse the process of hormonal resistance.

Interferons are known to have anti-tumor activity *in vitro* [5–8]. But despite early reports that leukocyte interferon produced partial responses in breast cancer [9, 10], the results of recent clinical trials using interferons as single-agent or adjuvant therapy for breast cancer have been disappointing [11, 12]. However, interferons affect a wide range of cellular functions and can modulate the ER in experimental systems. Both alpha and beta interferon have been reported to increase the ER activity in human breast cancer tissue [13] and in breast cancer cell lines [7, 14], although three studies have demonstrated either no change or a reduction in the ER of breast cancer cell lines incubated with alpha, beta, or gamma interferon [5, 6, 15]. Two *in vivo* studies have also reported conflicting results;

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the ER and progesterone receptor (PR) status of skin nodules from breast cancer patients increased with gamma interferon [16], but no change was seen in the ER or PR of endometrium from premenopausal women receiving leukocyte interferon [17].

If interferon can up-regulate the ER in breast cancer, adding interferon to antiestrogen therapy might increase the response rate or duration of response to hormonal therapy. This study evaluated the clinical role of alpha interferon in overcoming resistance to antiestrogen therapy in breast cancer.

Patient selection and methods

Patients with metastatic breast cancer who were ER-positive or ER-unknown were eligible for the study. Patients had to have clearly measurable disease and a Zubrod performance status < 3. All patients signed an informed consent according to institutional policy. Patients were excluded from the study if they had received TAM in the past but had been off TAM for greater than 1 month, had a previous or concurrent primary malignancy with the exception of carcinoma *in-situ* of the cervix or squamous cell carcinoma of the skin, or if metastatic disease involved greater than one-third of the liver.

Group I included patients who were showing evidence of disease progression after an objective response to TAM therapy, and IFN was added to TAM therapy. In addition, some patients with no prior history of TAM treatment who were ER-positive or ER-unknown received TAM plus IFN as front-line hormonal therapy (Group II).

All patients received a history and physical examination. Laboratory studies included a complete blood count, serum chemistries, and a carcinoembryonic antigen, and the extent of disease was documented by direct measurement or radiographically. ER and PR levels were obtained when possible.

All patients were either continued on (Group I) or started on (Group II) TAM at a dose of 10 mg orally twice daily. The initial dose of recombinant alpha interferon, Intron A (IFN), was 5.0 million units per meter squared (mu/m^2) intramuscularly, which was self-administered daily for five days each week. After the first 15 patients required dose reductions of IFN, the starting dose was decreased to 2.5 mu/m^2 daily for 5 days each week. The dose of IFN was reduced by 50% if a patient experienced $>$ grade 2 toxicity.

Patients were evaluated at least every 6 weeks for evidence of a response using the criteria defined by the UICC [18].

Table 1. Characteristics of patients treated with interferon and tamoxifen therapy

Characteristic	Number (%)
Sex	
Female	22
Male	1
Median age (years)	50
Race	
White (including Hispanic)	20
Black	3
Menopausal status	
Pre or peri	10 (45)
Post	12 (55)
Performance status	
0	7 (30)
1	11 (48)
2	3 (13)
3	2 (8)
Dominant disease	
Visceral	11 (50)
Soft tissue	5 (23)
Bone	6 (27)
Number of disease sites	
1	9 (41)
2	9 (41)
≥ 3	4 (18)
Estrogen receptor	
< 10(ER −)*	1 (4)
> 10(ER +)**	13 (59)
Unknown	8 (36)
Prior chemotherapy	
Adjuvant	6 (27)
Peri-operative	2 (8)
For metastatic disease	1 (4)

* Estrogen receptor negative.
** Estrogen receptor positive.

Results

Twenty-two women and one man with metastatic breast cancer were entered into this phase II study; 23 were evaluable for toxicity and 19 were evaluable for response. Four patients were considered inevaluable; 2 patients discontinued IFN early due to toxicity, 1 patient, in retrospect, did not have evaluable baseline disease, and one patient continued TAM/IFN but did not return here for follow-up.

Patient characteristics prior to entry into the study are shown in Table 1. Twenty patients were caucasian or hispanic and 3 were black. The age of the patients ranged from 27 to 76 with a median age of 50 years, and 78% had a Zubrod performance status of <2. Ten women were pre- and 12 were postmenopausal.

Of the 22 patients who had evaluable baseline disease, visceral disease was dominant in 50%, 27% had primarily bone disease, and 23% had soft tissue involvement; 59% had more than one site of disease. Thirteen patients were ER-positive, 1 was ER-negative (ER = 9) but had responded to TAM, and 8 were ER-unknown; 36% had received prior chemotherapy.

The major protocol toxicities (Table 2) included fatigue, myalgias, anorexia with weight loss, and fever. Depression or anxiety, alopecia, nausea and vomiting, and diarrhea were less common. Thrombocytopenia occurred in 3 patients and neutropenia with an absolute granulocyte count $<1.0\,mm^3$ was seen in 3 patients receiving the full dose. A slight rise in serum aspartate transaminase was observed in 5 patients, and 4-fold elevations were seen in 2 patients with a history of alcohol ingestion.

The first 15 patients were started on IFN at the dose of $5\,mu/m^2$. However, after IFN was discontinued in 2 patients after 2 weeks and dose reduction was required in an additional 10 patients, the starting dose was reduced to $2.5\,mu/m^2$. Dose and/or schedule reductions were also required in 4 of 8 patients started at this level. A total of 8 of 23 patients discontinued IFN due to toxicity after a median of 1 month (range 0.5 to 7.5) which was, in general, dose related. The dose of TAM remained unchanged and no unexpected toxicities occurred.

In Group I, the median duration of responsiveness to prior TAM therapy was 13 months (range 7 to 29 months), and there were no partial or complete responses seen with the addition of IFN to TAM. One patient had a minor response and 2 patients with stable disease at 1 month discontinued the therapy due to toxicity.

Table 2. Toxicity of tamoxifen plus interferon therapy (N* = 23)

	Grade				
	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
Fatigue/weakness	3 (13)	4 (17)	5 (22)	11 (48)	
Myalgias/arthralgias	9 (39)	9 (39)	5 (22)		
Anorexia/weight loss	7 (30)	3 (13)	12 (52)		
Fever/chills	5 (22)	6 (26)	12 (52)		
Depression/anxiety	10 (43)	4 (17)	7 (30)	2 (9)	
Alopecia	15 (65)	5 (22)	2 (9)	1 (4)	
Nausea/vomiting	8 (35)	8 (35)	6 (26)	1 (4)	
Diarrhea	15 (65)	3 (13)	4 (17)	1 (4)	
Hematologic					
Thrombocytopenia		3 (13)			
Neutropenia	10 (43)	5 (22)	2 (9)	2 (9)	1 (4)
Serum aspartate transaminase elevation	17 (75)	4 (17)	0	1 (4)	1 (4)

* Number.

Of the 10 evaluable patients from Group II, 2 achieved a complete response of 10+ and 19+ months duration and are continuing therapy, and 3 had a partial response for an overall response rate of 50% (95% confidence interval (CI) = 19–81%). One patient had a minor response, 3 patients had stable disease, and 1 patient progressed during 1 month of therapy. All 5 patients with objective responses were ER-positive, 3 of the 5 were PR-positive, and there were no responses among the 3 patients who were ER-unknown. One ER-positive patient had evidence of progressive liver disease after 1 month of TAM/IFN, but continued the therapy elsewhere with reportedly a complete response lasting 22 months which could not be confirmed radiographically. Including this patient would increase the response rate to 54%.

Overall, the median time-to-progression was 10+ months (range 7.5 to 19+) for responders, and 5 months (range 3 to 12 months) for those with stable disease on TAM/IFN.

Discussion

Up-regulation of the ER might overcome resistance to antiestrogen therapy and prolong the survival of patients with metastatic breast cancer. Although interferons have been shown to modulate the ER status *in vitro,* no clinical trials to assess the effect of IFN on tumor responsiveness to hormonal therapy have been published. This study demonstrated that the addition of IFN, as utilized in this study, does not appear to overcome TAM resistance in patients with metastatic breast cancer. In Group I, only 2 patients with tumor progression on TAM had short-term disease stabilization with the addition of IFN, and both of these patients had had a long disease-free-interval prior to the development of metastatic disease (41 and 64 months), suggesting that the modest benefit might only reflect the biological behavior of the tumor.

Group II demonstrated an overall response rate to TAM/IFN of 50% (CI = 19 to 81%), a 71% response rate for ER-positive patients (CI = 29 to 96%) and no responses in patients whose ER status was unknown. The published response rates to TAM for ER-positive tumors is 50 to 60%, ER- and PR-positive tumors is 70%, and ER-unknown tumors is 30% [2]. Given that 4 of the 5 responding patients had ER levels > 50 and 3 of the 5 were PR positive, both of which predict for TAM sensitivity, it is unlikely that the response rate to TAM/IFN was greater than that which would have been expected with TAM alone (5% rejection error) [19]; the data is insufficient to evaluate the impact of IFN on response duration. Although the CIs are wide, these results do not support the addition of IFN to overcome clinical TAM resistance.

There are several possible explanations for the lack of therapeutic advantage to adding interferon to overcome TAM resistance in breast cancer. First, although *in vitro* data suggests that alpha interferon can increase ER activity in breast cancer cells, there is no similar evidence *in vivo*. Unfortunately, no tissue was available to document modulations in the receptor status during therapy. Secondly, if IFN up-regulated the ER, it may not have been functional; hormonally insensitive breast cancer cells with abnormal receptors have recently been described [20]. And finally, it has been suggested that tumors contain heterogeneous mixtures

Table 3. Objective response rates to tamoxifen (TAM) plus interferon therapy by history of prior TAM exposure

	Prior TAM N = 10 number	No prior TAM N = 13 number (%)	95% CI[2]
Complete response (CR)	0	2	
Partial response (PR)	0	3	
Minor response	1	1	
Stable disease	2	3	
Stable disease but stopped due to toxicity	3	0	
Progressive disease	3	1	
Not evaluable	1	3	
Overall response rate (CR + PR)	0/9	5/10 (50%)	19–81
Response rate for ER[3] positive		5/7 (71%)	29–96
Response rate for ER unknown		0/3	

[1] does not include the patient with the undocumented CR.
[2] Confidence interval.
[3] Estrogen receptor.

of cells with different sensitivities to antiproliferative agents [21]. Hormonally insensitive breast cancer cell lines can have fully functional ERs where the response to antiestrogen therapy would be unrelated to receptor status [22, 23]. In addition, a heterogeneous breast cancer tumor model in mice suggests that it is the hormone-independent or interferon-insensitive elements that are responsible for therapeutic failures with these agents [24].

In conclusion, this phase II study did not demonstrate a therapeutic benefit of adding alpha interferon to TAM therapy in order to overcome TAM resistance in patients with metastatic breast cancer who had developed resistance while on TAM therapy or who had never been treated with TAM. However, the interactions between the hormone receptor status, antiestrogen therapy, and interferons are complex, and the role of interferon in the treatment of breast cancer remains to be defined.

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