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Original Paper

The Evidence for Tamoxifen and Chemotherapy as Treatment for Metastatic Melanoma

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Tamoxifen, an oestrogen antagonist routinely used in the treatment of breast cancer, has been used in clinical trials for patients with melanoma since the late 1970s. Following initial promise as a single agent for the treatment of metastatic melanoma, tamoxifen was first combined with chemotherapy in this setting in 1984. Since then, numerous phase II studies have combined tamoxifen with different chemotherapeutic agents, with some suggesting that tamoxifen significantly improves the efficacy of cisplatin-containing regimens. Overall response rates range from 8 to 60%. Several randomised trials also have been completed, with response rates of 12–30%. One such study showed statistically significant improvements in response rate and survival when tamoxifen was added to dacarbazine; however, other studies have not observed these benefits with the addition of tamoxifen to cisplatin-containing regimens. At present, the author's opinion is that the strength of evidence does not support the use of tamoxifen in combination with cisplatin-containing chemotherapy for the treatment of metastatic melanoma. Controversy remains as to whether the strength of evidence from the randomised trials outweighs the combined evidence from numerous nonrandomised trials. Resolution of this controversy may depend on the results of the North Central Cancer Therapy Group and/or a common agreement as to relative strength of evidence from clinical trials of different designs. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: tamoxifen, cisplatin, dacarbazine, carmustine, metastatic melanoma, randomised trials, chemotherapy
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INTRODUCTION

TAMOXIFEN IS an oestrogen receptor antagonist used routinely in the treatment of breast cancer. *In vitro* studies have suggested the presence of oestrogen receptors on melanoma cells and since the late 1970s, tamoxifen has been used in both single cohort and randomised clinical trials of patients with melanoma either as a single agent or in combination with other chemotherapeutic agents. This review provides a perspective on the use of tamoxifen in the treatment of metastatic melanoma.

SINGLE-AGENT TAMOXIFEN

In 1976, Fisher and associates reported the presence of oestrogen receptors (ER) on human melanoma cells derived from metastatic tumours [1]. Following a preliminary report by Nesbit and colleagues in 1979 that described objective responses to single-agent tamoxifen in 4 out of 26 metastatic melanoma patients [2], 12 phase II trials were conducted and evaluated in a meta-analysis by the European Organization for Research and Treatment of Cancer (EORTC) Malignant Melanoma Cooperative Group in 1982 [3–13]. While the overall response rate was only 7% (15/213), more women responded than men and the response rate for women 50 years of age or older was 25% (6/24). Despite these promising results, a subsequent phase II trial published in 1992 showed a response rate of only 4.9% (5/102) in postmenopausal women treated with tamoxifen 40 mg daily [14].

While the original report by Fisher and associates detected ER on 46% (16/35) of patients with melanoma [1], a subsequent trial of 18 patients treated with diethylstilbestrol showed two partial responses (11%), but neither was among the 4 patients whose biopsies demonstrated ER activity. The authors suggested that this lack of correlation ruled out a direct mechanism of action linked to ER activity and pointed

toward some indirect action not requiring ER [15]. Subsequent phase II studies by Creagan and coworkers [4] and Karakousis and colleagues [5] were clinically disappointing; in the former study, no objective responses were seen despite treatment with high-dose tamoxifen at 100 mg/m^2 [4]. McCarty and associates reported that the enzyme tyrosinase could mimic ER binding, leading to the possibility that this or other interfering substances could account for apparent ER activity and the failure to correlate this activity with response to tamoxifen [16]. To date, no further studies using single-agent tamoxifen in this setting have been published.

IN VITRO SYNERGISM BETWEEN TAMOXIFEN AND CISPLATIN

In 1984, Del Prete and colleagues reported the results of the first clinical trial combining cytotoxic chemotherapy with tamoxifen in patients with metastatic melanoma [17]. In their single cohort phase II study, 55% (11/20) of patients achieved a complete response (CR; 4/20) or partial response (PR; 7/20) with the combination of carmustine (BCNU) 150 mg/m^2, dacarbazine (DTIC) 220 mg/m^2, cisplatin 25 mg/m^2, and tamoxifen 10 mg orally twice daily. Tamoxifen was administered continuously throughout the cycle. DTIC and cisplatin were given over 3 days every 3 weeks in 6-week cycles and carmustine was given on day 1 only. McClay subsequently reported similar results with this regimen; an overall objective response rate of 50% (10/20) was observed, with a CR rate of 15% (3/20) [18]. However, a high rate of deep vein thrombosis (DVT; 6/20) and pulmonary embolism (PE; 4/20) was encountered.

As a result of these findings, McClay and associates sought experimental evidence for this apparent clinical improvement associated with tamoxifen in combination with chemotherapy [19]. Thus, the ability of tamoxifen to modulate the sensitivity of a human melanoma cell line to cisplatin was tested. Following the administration schedule used in clinical studies, the authors exposed the cells to tamoxifen for 24 hours, followed by cisplatin and tamoxifen for 1 hour and then assayed the cells in the presence of tamoxifen alone. Tamoxifen significantly lowered the 50% inhibitory concentration (IC_{50}) when combined with cisplatin compared to tamoxifen alone (2.98 mcM versus 0.38 mcM, respectively; $P < 0.03$). In addition, tamoxifen and cisplatin were synergistically inhibitory and this synergy appeared to be dependent on the sensitivity of the cells to tamoxifen rather than cisplatin; that is, cells sensitive to tamoxifen showed synergistic inhibition when exposed to both agents together. Interestingly, combining tamoxifen with DTIC or carmustine resulted in a moderate antagonistic effect compared to the cytotoxic agents alone. Subsequent studies have suggested that concurrent exposure of melanoma and ovarian cancer cell lines to tamoxifen and cisplatin may delay the development of resistance to cisplatin [20] and that the resistance to tamoxifen, which abolished synergy with cisplatin, is associated with inhibition of apoptosis [21].

TAMOXIFEN IN COMBINATION WITH CHEMOTHERAPY

Nonrandomised trials

Response rates reported from clinical trials of tamoxifen and chemotherapeutic agents for metastatic melanoma (with or without historical controls) since 1991 are presented in Table 1. In an effort to confirm the results of their initial study, McClay and associates treated two subsequent and consecutive cohorts of patients, the first received cisplatin alone and the second received cisplatin plus tamoxifen. The response rate was 10% in the first cohort but increased to 52% after tamoxifen was reintroduced [22]. The authors' cumulative experience with 45 patients receiving chemotherapy plus tamoxifen and 20 patients receiving chemotherapy alone showed an overall response rate of 51% with tamoxifen and an overall response rate of 10% without tamoxifen [23]. Berd and colleagues treated 15 patients with BCNU, DTIC and cisplatin (BDP) plus high-dose tamoxifen (160 mg/day for 7 days prior to beginning chemotherapy). The response rate was 47% and there was no evidence of DVT or PE [24]. In a small study of 10 patients, Tan and Ang recently reported a response rate of 60% with BDP and tamoxifen 40 mg daily [25].

Lattanzi and coworkers also treated consecutive cohorts of patients with metastatic melanoma using BDP with and without tamoxifen; however, cycles were repeated every 8

Table 1. *Nonrandomized trials of tamoxifen and chemotherapy since* 1991

Reference	Regimen	*n* (evaluable)	Overall response rate (%)*
Tan 1996 [25]	BDP + TAM 40 mg/day	10	60
Lattanzi 1993 [26]	BDP versus	16	25
	BDP + TAM	26	54
Richards 1992 [27]	DP + TAM	20	50
Fierro 1993 [28]	BDP + TAM	32	47
Saba 1993 [29]	BDP + TAM	48	38
Foshag 1993 [30]	BDP + TAM	60	47
Feliu 1996 [32]	P 100 mg/m^2 + TAM 120 mg/day	31	16
Flaherty 1993 [33]	D 750 mg/m^2 + P 100 mg/m^2 versus	39	13
	Same + TAM 20 mg/day	55	18
Bajetta 1993 [34]	C 350 mg/m^2 + cytarabine 150 mg/m^2 versus	21	19
	Same + TAM 40 mg/day	25	8
McClay 1993 [35]	1] P 100 mg/m^2	24	13
	2] P 100 mg/m^2 + TAM 160 mg day 1, 20 mg/day for 3 weeks	19	16
Antoine 1995 [37]	P + IL-2 + IFN + TAM	22	41
	P + IL-2 + IFN	39	54
Schultz 1993 [38]	BDP + IFN + TAM 200 mg/day for 5 days, then 40 mg/day	22	29

P, cisplatin; TAM, tamoxifen; D, dacarbazine; C, carboplatin; M, male; F, female; B, carmustine; IFN, interferon alpha; IL-2, interleukin 2.
*Complete and partial responses.

weeks. In a recent 5-year follow-up, they reported a response rate of 54% for tamoxifen-treated patients and 25% for chemotherapy alone. Additionally, survival was prolonged for tamoxifen-treated patients [26]. Richards and associates treated 20 consecutive patients who had progressed after receiving interleukin-2 (IL-2) and/or prior chemotherapy [27]. Therapy with DTIC, cisplatin and tamoxifen achieved a PR rate of 50% in these heavily pretreated patients. In a study of 32 patients with metastatic melanoma, Fierro and colleagues reported a CR rate of 16% and PR rate of 31% using BDP and tamoxifen [28]. In addition, females in this study had a significantly improved median survival in comparison with males (10 versus 7 months, respectively; $P < 0.025$). In another cohort study of 57 patients, Saba and coworkers investigated the same regimen for 6 cycles. Of 48 patients who accepted treatment, a response rate of 38% was achieved [29]. The 9 patients who refused treatment were followed as untreated controls. At 300 days of follow-up, a significantly larger proportion of patients were alive in the treated group (70% versus 31%, respectively; $P < 0.0004$), although the validity of such controls may be questioned. In one of the largest single cohort studies to date, Foshag and associates treated 60 patients who had progressed following treatment with an allogeneic melanoma cell vaccine. After receiving BDP and tamoxifen, 47% of these patients responded and 22% experienced a CR [30].

Not all prospective cohort studies combining tamoxifen with chemotherapy have suggested an advantage with the addition of tamoxifen in this patient population. Buzaid and colleagues combined high-dose cisplatin 50 mg/m^2 and DTIC 350 mg/m^2 on days 1–3 every 4 weeks with high-dose tamoxifen (200 mg daily for 7 days before starting chemotherapy, then 20 mg daily throughout the cycle) [31]. Among 23 evaluable patients, the overall response rate was only 13%. For the historical controls who received the cisplatin-DTIC regimen alone, a response rate of 17% was observed. Feliu and associates evaluated 31 patients treated with cisplatin 100 mg/m^2 every 3 weeks and tamoxifen 60 mg twice daily (every 12 hours) for 3 weeks. A response rate of 16% was achieved; thus, the authors did not recommend this regimen for the treatment of metastatic melanoma [32]. Flaherty and colleagues reported similar results with DTIC 750 mg/m^2 and cisplatin 100 mg/m^2 with tamoxifen 20 mg daily throughout the cycle. Only 18% of patients responded to tamoxifen in the combination regimen compared to 13% (5/39) of historical controls who received cytotoxic chemotherapy alone [33].

Other chemotherapeutic agents also have been combined with tamoxifen for the treatment of metastatic melanoma. Bajetta and coworkers treated two groups of patients sequentially; the first group received carboplatin and cytarabine alone and for the second group, tamoxifen 40 mg daily was added throughout the cycle. Of 21 evaluable patients in the first group, 19% (4/21) responded. In contrast, 8% (2/25) of patients responded in the tamoxifen-treated group. All patients had received prior chemotherapy and/or immunotherapy [34]. In an attempt to confirm synergism between tamoxifen and cisplatin and to overcome clinically established cisplatin resistance, McClay and associates treated 24 metastatic melanoma patients with cisplatin 100 mg/m^2 every 3 weeks; 13% of patients responded. Those who failed to respond clinically (cisplatin resistant) were then treated with the same dose of cisplatin plus tamoxifen 160 mg on day 1, followed by 20 mg daily throughout the 3-week cycle. In 19 assessable patients, 16% achieved a CR or PR as conventionally defined; however, when the authors included mixed responses, the overall response rate (32%) was statistically significantly different ($P < 0.001$) [35]. In a recent phase I study, McClay and associates treated successive cohorts of patients with escalating doses of tamoxifen and weekly cisplatin 80 mg/m^2. Patients received up to 320 mg/m^2 at the time of the report with no patients responding at doses less than 240 mg/m^2 [36]. No DVTs were evident at any dose levels.

Chemoimmunotherapy. At least three studies have combined chemotherapy, immunomodulators and tamoxifen. Antoine and coworkers added tamoxifen to a regimen of cisplatin, IL-2, and interferon alpha (IFN-α). The response rate with tamoxifen was lower than the response rate observed without tamoxifen in a previous study (41 versus 54%, respectively) [37]. Schultz and associates combined BDP, IFN-α and tamoxifen in a phase II study of 22 patients. Tamoxifen was given as a loading dose (200 mg/day for 5 days) prior to the initiation of chemotherapy, followed by 40 mg daily during the remainder of the 4-week cycle. Myelosuppression, particularly thrombocytopenia, was severe. The response rate was 29% [38]. Similarly, Rixe and colleagues treated 91 patients with high-dose cisplatin, IL-2, IFN-α and tamoxifen. The trial was stopped prematurely due to an increased frequency of sepsis and because response rates were similar to those observed in historical controls who did not receive tamoxifen [39].

Megestrol acetate, a synthetic progestin that has been shown to decrease P-glycoprotein-mediated efflux of some multidrug resistance-associated agents, also has been combined with BDP chemotherapy. Among 18 evaluable metastatic melanoma patients, Nathanson and coworkers reported a response rate of 55% with megestrol acetate [40]. As with tamoxifen, these promising results require confirmation in a randomised trial.

Randomised trials

Response rates of tamoxifen combined with chemotherapy in randomised trials are presented in Table 2. The first randomised trial comparing chemotherapy alone with chemotherapy and tamoxifen was published in 1992 by Cocconi *et al.* [41]. 117 patients were randomised to receive DTIC 250 mg/m^2/day for 5 days every 3 weeks alone or with tamoxifen 20 mg/m^2/day for 3 weeks. Of 52 evaluable patients receiving DTIC alone, 12% responded, whereas 28% (17/60) of those receiving DTIC and tamoxifen responded. Similarly, survival was prolonged for those who received tamoxifen (48 versus 29 weeks, respectively). These differences were statistically significant ($P = 0.03$ and $P = 0.02$, respectively). No DVTs were reported. When analysed by gender, the difference in response rate for women was statistically significant in favour of tamoxifen ($P = 0.04$); however, the difference in response rate for men was not. In an accompanying editorial, the validity of the results was questioned due to (1) the poor response rate in the DTIC group; (2) small size of the trial; (3) inclusion of a high proportion of patients with only local or regional disease; (4) lack of information regarding the delivered dose of treatment; (5) minimal attention given to toxicity and quality of life; and (6) potential for maldistribution of prognostic factors [42].

Table 2. Randomized trials of tamoxifen and chemotherapy

Reference	Regimen	*n* (evaluable)	Overall response rates (%)	*P*-Value
Cocconi 1992 [41]	D 250 mg/m^2 for 5 days versus	52	12	
	Same + TAM 20 mg/m^2/day	60	28	0.03
Legha 1993 [43]	PVD + IFN versus	36	47	
	Same + TAM 20 mg/day	33	30	ND
Ferri 1994 [44]	C 300 mg/m^2 + D 1000 mg/m^2 versus	26	19	
	Same + TAM 20 mg/day	25	12	NS
Rusthoven 1996 [45]	BDP versus	97	21	
	BDP + TAM 160 mg/day for 7 days, then 40 mg/day	98	30	0.19

D, dacarbazine; TAM, tamoxifen; P, cisplatin; V, vinblastine; IFN, interferon alpha; C, carboplatin; B, carmustine; ND, not determined; NS, not significant.

Legha and colleagues conducted a randomised trial of 69 patients that compared cisplatin, vinblastine, DTIC (CVD) and IFN with or without tamoxifen in conventional doses. While 47% responded without tamoxifen, only 30% in the tamoxifen group responded. The trial was closed because the investigators predicted that it was statistically unlikely ($P < 0.005$) that a predetermined, clinically meaningful response rate of 55% would be observed in the tamoxifen group if more patients were accrued [43]. Ferri found no significant difference in the response rates of 51 evaluable patients who were randomised to receive carboplatin 300 mg/m^2 and DTIC 1000 mg/m^2 every 4 weeks with or without tamoxifen 20 mg daily (12 versus 19%, respectively) [44].

More recently, we reported the results of a randomised study of 211 patients that was conducted by the National Cancer Institute (NCI) of Canada Clinical Trials Group [45]. Metastatic melanoma patients received BCNU 150 mg/m^2 on day 1, DTIC 220 mg/m^2 and cisplatin 24 mg/m^2 daily on days 1–3 and 22–24, and tamoxifen 160 mg/m^2 daily for 7 days followed with 40 mg daily or placebo. Patient characteristics were well balanced between treatment groups. Among 195 patients evaluable for response, the overall response rate was 30% in the tamoxifen group and 21% in the placebo group ($P = 0.19$; two-sided test). There was no difference in the rate of DVT ($P = 0.53$) or PE (none detected in either group); similarly, the frequency of febrile neutropenia and grade 4 neutropenia and/or thrombocytopenia were not significantly different between groups. The delivered dose intensity was equally high in both groups, ranging from 83 to 88% for each drug. Unlike the study by Cocconi *et al.*, the response rates between men and women were similar (24 versus 28%, $P = 0.67$). Disease-free and overall survival were not significantly different between the groups. The authors concluded that, in this unselected population with metastatic melanoma, tamoxifen did not significantly improve the efficacy of the BDP combination chemotherapy regimen.

TAMOXIFEN FOR METASTATIC MELANOMA: WHAT IS THE STRENGTH OF EVIDENCE?

As shown above, considerable evidence has accumulated over the last 15 years both for and against the use of tamoxifen in this setting. Nonrandomised and randomised trials have provided support for both sides. In a recent review, McClay and McClay have stated their support for randomised trials as the gold standard for design of clinical studies [46]. However, they also express concern that accepting the results of the Canadian study as correct '... ignores a much greater experience with this regimen in a wide variety of institutions with a greater number of patients' [46]. This refers to the cumulative, nonrandomised, often single cohort data as well as the *in vitro* data that supports synergy between tamoxifen and cisplatin [19–21]. Yet, the authors fail to provide convincing reasons for disbelieving the results of the Canadian trial although even the best designed randomised trials usually have a predetermined chance of type II error. Their suggestion that genetic differences account for the low response rates in the latter trial is interesting but without foundation.

The schema of Cook and coworkers is recognised and used internationally as criteria for weighing the importance of different trials based primarily on their relative risk of yielding biased results [47]. In this schema, the randomised trial and the meta-analysis are considered the most reliable designs, followed by cohort studies with nonrandomised but contemporaneous controls. While confirmation of the Canadian trial would be important (a randomised trial by the North Central Cancer Treatment Group (NCCTG) of similar design and magnitude as the Canadian study has been completed and its results will be available soon), it remains for the clinician to decide whether the results of a specified number of successive cohort studies of varying designs, differing patient characteristics and different institutions weigh more heavily than the results of a single, well-conducted randomised trial. At this time, no further studies in this area are planned among national and international cooperative groups including the NCI Canada Clinical Trials Group. As for the other randomised trials, the trial by Cocconi and associates seems to demonstrate the efficacy of tamoxifen when combined with DTIC. However, the methodological issues mentioned previously have raised questions about the validity of the results. The small randomised trials by Legha and colleagues [43] and Ferri and coworkers [44] used platinum-based regimens and did not show additional efficacy when tamoxifen was included.

So, is tamoxifen efficacious when combined with chemotherapy in the treatment of metastatic melanoma? Ultimately, the answer depends on what one believes is the best evidence available. This may differ among institutions and individual clinicians. For example, a survey of the investigators who contributed to the Canadian study was conducted following study completion. Thirteen of 20 investigators responded. Despite the study results and the conclusion that tamoxifen did not improve the efficacy of chemotherapy alone, two respondents stated that they continued to use tamoxifen with cisplatin and DTIC and four respondents

stated that they used BDP plus tamoxifen for the treatment of metastatic melanoma. Four of six investigators also stated that they used chemotherapy alone in some patients and added tamoxifen to chemotherapy for selected patients, such as younger women and severely ill patients for whom a rapid response was desired. In addition, this survey highlights some of the additional factors that modulate evidence-based clinical decision making, including the availability of local resources, cost, patient insistence on a certain treatment and medical-legal concerns. While the Canadian study was designed to be generalisable to all patients with metastatic melanoma, the relatively low risk of toxicity with tamoxifen may encourage some clinicians to use tamoxifen in selected patients despite the overall negative result. Differences in study interpretation are common in oncology; such differences may be best resolved through the development of practice guidelines where all of the available evidence is tabled and collectively discussed.

CONCLUSIONS

The efficacy of tamoxifen in the treatment of metastatic melanoma has been evaluated in a number of phase II nonrandomised trials. Despite initial promise as both a single agent and in combination with chemotherapy, the routine use of tamoxifen in combination with cisplatin-containing chemotherapy for metastatic melanoma is not supported currently by randomised trial data. While tamoxifen may add to the efficacy of DTIC alone in this setting, the response rate of the combination may not exceed that of cisplatin-containing chemotherapy alone. It remains unclear whether some subgroups of patients may benefit from the addition of tamoxifen to chemotherapy. The NCCTG study results will provide further information regarding the potential benefits of tamoxifen in patients with metastatic melanoma. Using the hierarchy of evidence proposed by Cook and associates, it is the view of the author that the weight of evidence does not support the use of tamoxifen in this setting at this time.

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