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Tamoxifen in the treatment of recurrent ovarian carcinoma

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Abstract

This review examines the evidence for useful clinical activity of tamoxifen in women with ovarian carcinoma who have failed conventional cytotoxic chemotherapy. The optimised search strategy of the Cochrane Gynaecological Cancer Collaborative Review Group by Williams was used. Tamoxifen demonstrates a modest degree of effectiveness in ovarian cancer refractory to cytotoxic chemotherapy. The overall objective response rate in all trials (647 patients) was approximately 11%. There is, however, a wide variation in the objective response rates in the different trials (0–56%). Tamoxifen therapy has limited efficacy in refractory ovarian carcinoma. However, considering the mild toxicity of tamoxifen, occasional long-term palliation and lack of alternatives, the drug has a useful role in heavily pretreated patients with ovarian cancer.

Keywords: Anti-oestrogen; Ovarian cancer; Palliation; Salvage therapy; Tamoxifen

1. Introduction

Ovarian cancer causes more deaths from cancer than any other type of gynecological cancer. This is partly because 60–70% of patients present with advanced disease that is widespread within the abdominal cavity. The other factor is the relative lack of effectiveness of drug therapy for advanced disease [1]. Although primary therapy may be curative there is no convincing evidence that any salvage programme can reach this goal. For the large majority of patients who either fail to achieve a complete remission or relapse after achieving one, the situation becomes much more tragic. While response to second-line chemotherapy is not unusual, responses tend to be brief and long-term survival is rare [1]. New treatment and new drugs may be useful for arresting ovarian cancer that is no longer responsive to conventional drugs. Therefore, palliative treatment should be focused on optimising quality of life and delaying the time to the development of symptoms.

Ovarian cancer cells have been shown to possess surface receptors for oestrogen, progesterone and androgen and, *in vitro*, respond to tamoxifen and other hormonal agents [2]. The anti-oestrogen tamoxifen has many advantages, being an oral agent with an extremely favourable toxic profile. *In vitro* studies demonstrated direct antiproliferative activity of tamoxifen in ovarian carcinoma specimens. Moreover, tamoxifen has been shown to delay the development of resistance to cisplatin *in vitro* for an ovarian carcinoma cell line [3]. We have reviewed to our knowledge, all phase 2 and 3 trials of tamoxifen in advanced and recurrent ovarian carcinoma where patients failed on conventional cytotoxic drugs.

We have used the same selection criteria for inclusion and exclusion of patients as Williams [4]. The selection criteria by the authors have varied quite considerably. Some studies appeared to include only patients who were truly refractory to chemotherapy while some appeared to include some patients who had relapsed, but may not have been refractory to chemotherapy. We did not find any randomised control trials of tamoxifen versus best supported care. All reviewed trials failed to collect data on the palliative effects of tamoxifen. A number of trials [5–7] reported on the prognostic significance of the presence of hormonal receptors in the tumour, but there was no evidence that hormone receptor status could be used as a predictor of response to subsequent tamoxifen therapy [8]. The only data that could be analysed in the review were the response rates in the different trials. Reported response rate ranged from 0 to 56% (Table 1).

Overall, 72 of 633 patients (11%) responded objectively using different criteria in the various trials. We were, therefore, interested to retrospectively analyse a large series of unselected patients and present 155 individuals with recurrent ovarian cancer from The Norwegian Radium Hospital treated with tamoxifen.

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Table 1
Tamoxifen in refractory ovarian cancer

Author [Ref.]	Tamoxifen (dose day^{-1}) (mg)	*n* patients	Response rate (CR + PR) (%)
Schwartz [9]	20	13	1 (8)
Landoni [10]	40	55	0
Shirey [11]	20–40	22	0
Slevin [12]	40	22	0
Weiner [13]	20	31	3 (10)
Belinson [14]	20[a]	19	0
Markman [15], Hatch [16]	40	102	17 (17)
Osborne [17]	40	53	1 (0.2)
Pagel [18]	Not stated	29	8 (28)
Hammerlynck [19]	40	36	2 (6)
Cambell [20]	20	13	1 (8)
Rowland [21]	20	9	0
Jakobsen [22]	30[b]	17	0
Ahlgren [23]	40	29	5 (17)
Jäger [24]	30	37	0
Van Der Velden [25]	40	30	2 (7)
Genntas [26]	40	50	28 (56)
Present study (evaluable for response)	30–40	66	4 (6)
Total		633	72 (11)

[a] Combination with megoestrol acetate (160 mg day^{-1}).
[b] Cyclic hormonal treatment including medroxyprogesterone acetate (400 mg).

2. Patients, methods and results

155 patients with chemotherapy resistant recurrent ovarian carcinoma were treated with tamoxifen (30 mg or 40 mg daily). In the 66 patients evaluable for response there were 2 complete responders and 2 partial responders (6%). Disease was stabilised in the majority of evaluable patients (77%). Median survival time after initiation of tamoxifen treatment for the 155 patients was 4 months (95% CI: 3.3–5.4), and response to treatment was not associated with significantly improved prognosis since patients with complete or partial response and stable or progressive disease had a median survival time of 6.2 months and 5.5 months, respectively. Estimated 5-year survival rate was 2% (Fig. 1).

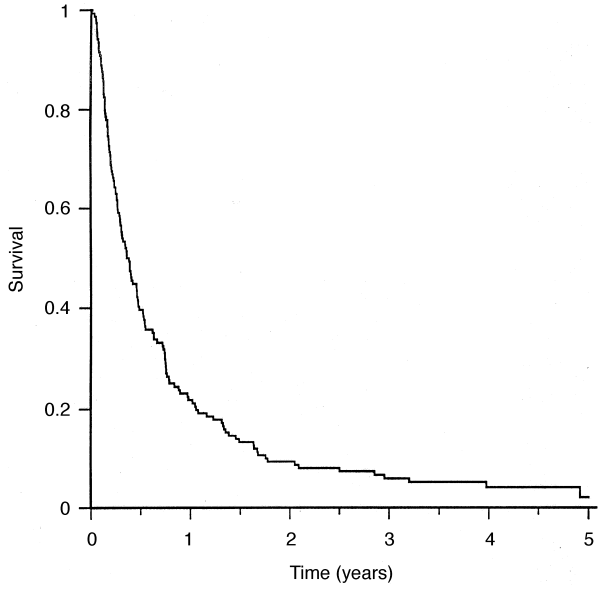

Fig. 1. Survival of patients with chemoresistant ovarian carcinoma treated with tamoxifen. Observation time is calculated from the initiation of tamoxifen treatment.

Survival of patients after initiation of tamoxifen was dependent on histological classification (clear-cell carcinoma versus other), FIGO stage and patient's age. Tumour differentiation, number of prior chemotherapeutic regimens, response to prior cisplatin treatment, classification of tumour regarding platinum-sensitivity, prior radiotherapy and dose of tamoxifen were not statistically significant.

3. Discussion

Several studies have been undertaken to investigate the usefulness of tamoxifen in the treatment of recurrent ovarian cancer (Table 1) [4,8]. The mean response rate in 633 patients published was 11%. Our results are in agreement since we observed a response rate of 6%. Patients with clear cell carcinoma were distinguishable from those with other histological types being associated with a poor prognosis. None of the 8 patients with such tumours in our study survived longer than 5 months after initiation of tamoxifen treatment. It is interesting to note, that tamoxifen induced in endometrioid adenocarcinomas a high response rate. Although

this tumour-type was diagnosed in only a small fraction of patients, 3 of 4 responders were patients with endometrioid adenocarcinomas. This strongly suggests that endometrioid adenocarcinoma may behave in a similar way as endometrial adenocarcinoma as hormone-sensitive tumours. In view of this finding, the possible risk of hormone-replacement therapy containing oestrogens should be discussed.

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Toremifene: where do we stand?

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