Anti-Cancer Drugs 2001, **12,** pp. 719–724

Clinical report

Phase II study of high-dose megestrol acetate in platinum-refractory epithelial ovarian cancer

Sarikapan Wilailak,[1] Vasant Linasmita[1] and Somkeart Srisupundit[1]
[1]Department of Obstetrics & Gynaecology, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.

Our objective was to determine the efficacy of megestrol acetate in the treatment of platinum-refractory epithelial ovarian cancer (EOC), and to evaluate the toxicities and quality of life (QOL) associated with this therapy. Patients with platinum-resistant epithelial ovarian cancer were treated with megestrol acetate (800 mg/day) orally for 28 days and then 400 mg/day for a minimum of 28 days before being assessed ready for evaluation of response to therapy. Patients who demonstrated a complete response (CR), partial response (PR) or stable disease were continued in the study until there was objective evidence of disease progression. All patients who went off study were followed up at regular intervals, every 2 months, to assess overall survival. Thirty-six patients were enrolled. Response was observed in seven of 36 patients (three CR and four PR). The response rate was 19.4% (95% CI 9–36). Four of the responders had the endometrioid cell type, while two were clear cell carcinoma and one was serouscystadenocarcinoma. All three CR patients had the histology of endometrioid carcinoma with the tumors located in the pelvis. Median survival of the study population was 5.8 months. Median survival in the responders was 12 months, while median survival in the non-responders was 5.5 months. Median progression-free survival in the responders was 8.3 months, while median progression-free survival in the non-responders was only 2 months. The majority of patients gained weight and had a fair quality of life score during treatment. The only toxicity observed was alopecia (grade 1) in four patients. We conclude that megestrol acetate has modest but definite activity in patients with platinum-refractory EOC, particularly in a small subset of the endometrioid subtype with limited disease in the pelvis. Only minimal toxicity was observed and the patients had a fair QOL score during the treatment. [© 2001 Lippincott Williams & Wilkins.]

Key words: Megestrol acetate, ovarian cancer.

Megestrol acetate was a gift of Bristol-Myers Squibb, Thailand.

Correspondence to S Wilailak, Department of Obstetrics & Gynaecology, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.
Tel: (+662) 201-1451; Fax: (+662) 201-1416;
E-mail: raswl@mahidol.ac.th

Introduction

Despite the introduction of platinum-based chemotherapy, the epithelial ovarian cancer (EOC) death rate remains high among gynecologic cancers. Between 70 and 80% of patients with advanced EOC will initially have a response to platinum-based chemotherapy, but resistance and progression will ultimately develop in 60–80%.[1,2] Second- or third-line chemotherapy is often poorly tolerated and lengthy remissions are infrequent.

Hormonal manipulation has been demonstrated to be relatively non-toxic and an effective palliative modality in tumors that arise from tissues under hormonal control. Both the estrogen receptor (ER) and progesterone receptor (PgR) have been identified in several studies of primary and recurrent ovarian carcinomas. Using various cut-off levels of cytosolic receptor (>10 to >50 fmol/mg protein), these studies have shown ER positivity in 37–69% of ovarian carcinomas and PgR positivity in 30–68%.[3–14] *In vitro* assays have also shown a significant reduction in colony formation when ER- and PgR-positive ovarian cancer cells are cultured with either progestational agent.[15]

Geisler, using megestrol acetate (800 mg/day) for 30 days and then maintaining use with 400 mg/day in recurrent or refractory ovarian cancer, found a response rate of 43%.[16] Sikic, in the same trial, observed an 8% response rate and an additional 6% minor remissions.[17] These attracted our attention and motivated the authors to perform a study using high-dose megestrol acetate in refractory EOC.

The aims of this study are to determine the efficacy of high-dose megestrol acetate in the treatment of platinum-refractory EOC, and to evaluate the toxicities and quality of life (QOL) associated with this therapy.

Materials and methods

Patient eligibility

Patients had to have (i) histologically proven EOC, (ii) platinum resistance, (iii) measurable disease, (iv) Zubrod performance status grade 0–2, (v) expected survival of >2 months, (vi) absolute granulocyte count $>1500/\mu l$, platelet count $>100\,000/\mu l$, Hb >8.5 g/dl, (vii) >4 weeks from the last chemo/radiation therapy, (viii) no serious concomitant medical conditions, (ix) no prior history of allergic reactions to progesterone and (x) no bowel obstruction or inability to absorb oral medication. All patients gave written informed consent.

Treatment plan

Subjects were treated as outpatients, and received 800 mg/day of megestrol acetate orally for 28 days and then 400 mg/day for a minimum of 28 days. Patients were evaluated for response at the end of the 8-week treatment period. Those patients with a complete response (CR), partial response (PR) or stable disease (SD) and acceptable toxicity would continue on treatment with 400 mg of megestrol acetate daily. The therapy would terminate when objective disease progression was observed or unacceptable toxicity appeared, or 8–12 weeks after obtaining CR. Before each 4-week period, careful evaluation was done for response and toxicity. Tumor measurements were reassessed after every 8–12 weeks of treatment by computed tomography scan or ultrasound. The subjects were followed for a minimum period of 12 months or until death. QOL was evaluated in every patient every 4 weeks using the questionnaire of the Manitoba Cancer Treatment & Research Foundation Functional Living Index—Cancer (FLIC),[18] which contains 22 questions, translated into the Thai language. The patients were required to respond by placing a slash mark on a visual analog scale divided into seven equal intervals. The questions on the FLIC are geared to assess the overall functional quality of a cancer patient's day-to-day life, including concerns related to pain and stress as well as the ability to work and do household chores. This study was approved by the Department of Obstetrics and Gynecology, Ramathibodi Hospital, Mahidol University.

Definitions

The definitions of CR, PR, SD and progressive disease (PD) were based on WHO criteria for reporting results of cancer treatment.[19]

Platinum resistance was defined as disease progression during or within 6 months of the most recent platinum treatment.[20,21]

Progression-free interval was defined as the duration from the date of first treatment until evidence of progression or relapse was noted.

Survival was measured from the date of first treatment to date of death.

Toxicities were defined according to WHO toxicity criteria. Unacceptable toxicity was any toxicity of a severity grade 3 or above, except for alopecia.

Standard statistical methods were used for data analysis. Probability of survival and progression-free survival were calculated according to the life-table method of Kaplan and Meier.[22]

Results

During the period from October 1995 to September 1998, there were 36 patients recruited. At that time, there were other second-line chemotherapy regimen implemented parallely, therefore the recruitment time of this study was relatively long. Patient characteristics are summarized in Table 1. The median age was 49.5 years and the median weight was 49.75 kg. The majority of the patients had a Zubrod performance status of 2. The most common FIGO staging was stage III. The histologic types are given in Table 1. There were three CR and four PR among the 36 patients. The overall objective response rate was 19.4% (95% CI 9–36%). Concerning the histopathology of the tumors among the seven responders, four were endometrioid carcinoma, two were clear cell carcinomas and one was a serous carcinoma. All three CR had the histology

Table 1. Patient characteristics (n=36)

Age [years; median (range)]	49.5 (27–59)
Weight [kg; median (range)]	49.75 (35–70)
Zubrod performance status (*N*)	
0	1
1	13
2	22
FIGO staging (*N*)	
I	5
II	5
III	18
IV	8
Histologic type (*N*	
serous	7
mucinous	8
clear cell	10
endometroid	9
poorly differentiated adenocarcinoma	2

of endometrioiod carcinoma and the tumors were located in the pelvis. The other four PR had tumor in the pelvis, pelvis and abdomen, liver and pelvis and lungs. The median survival of the study population was 5.8 months (Figure 1). The median survival of the responder was 12 months and that of the non-responders was 5.5 months (Figure 2). The median progression-free survival of the responders was 8.3 months and that of the non-responders was 2 months (Figure 3). One of the CR patients is currently still alive without disease after 3 years. Concerning the side effects or toxicity, 30 of the 36 patients showed a weight gain (not related to edema) varying from 0.5 to 25 kg. Four patients had a weight gain of more than 20%. No thromboembolism occurred in the study population. No clinical secondary adrenal suppression was observed. Only grade 1 alopecia was observed in four patients. Figure 4 shows a graph of the median QOL score (FLIC) which shows that the majority of the study population obtained a fair QOL score of around 90 (the possible minimum score is 7 and the possible maximum score is 154).

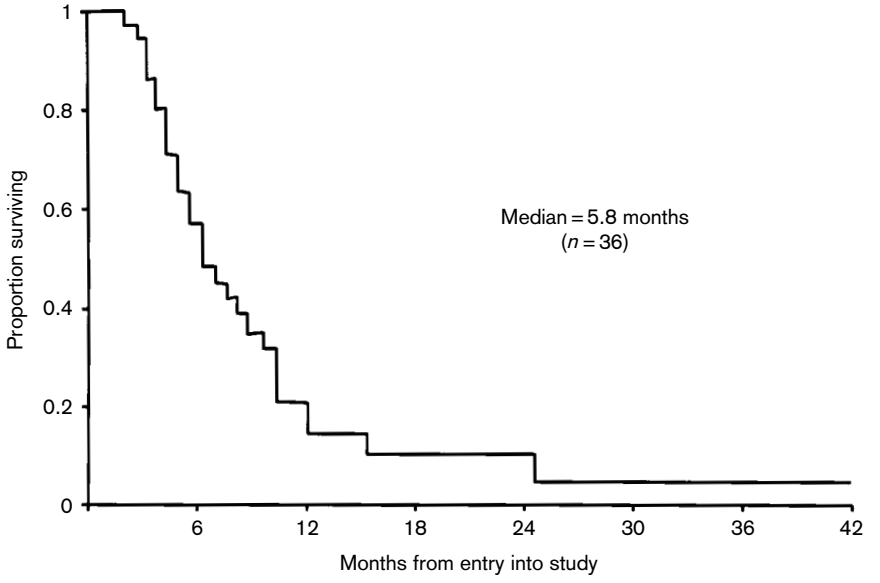

Figure 1. Survival curve of the entire study population.

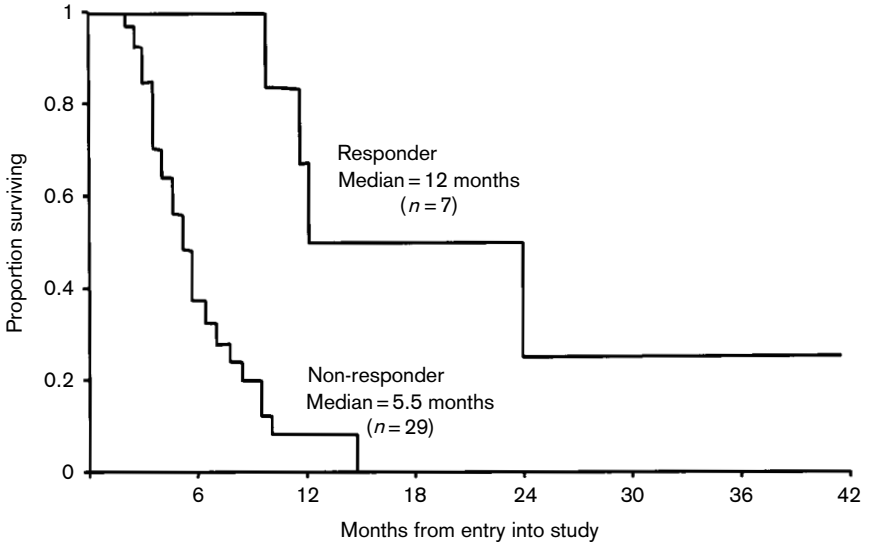

Figure 2. Survival curve of the responders and non-responders.

Discussion

Megestrol acetate therapy for EOC has been reported in several studies. Response rates in these reports ranged from 0 to 43%.[16,17,23–25] Differences in the study population and response criteria may account for some of the variation in response rates in these reports.

Megestrol acetate therapy is attractive due to its relatively non-toxic and facile administration. We used a high dose of megestrol acetate (800 mg/day) for 28 days followed by 400 mg/day. The response rate of 19% was quite low; however, CR was obtained. It is interesting that all three patients who achieved CR in this study had the histology of endometrioid carcinoma and tumors located in the pelvis. The subgroup of ovarian cancers with endometrioid histology appears to have a higher level of receptors, particularly PgR. At the other extreme, mucinous tumors show no tendency of having positive ER- or PgR-binding sites. Serous tumors occupy the place in between, with ER-binding sites present in some.[26] Thus the endome-

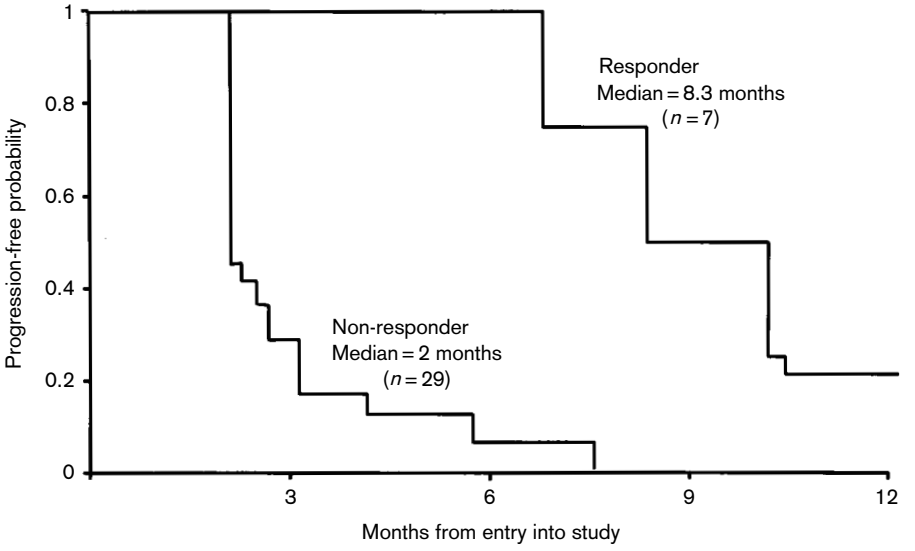

Figure 3. Progression-free survival curve of the responders and non-responders.

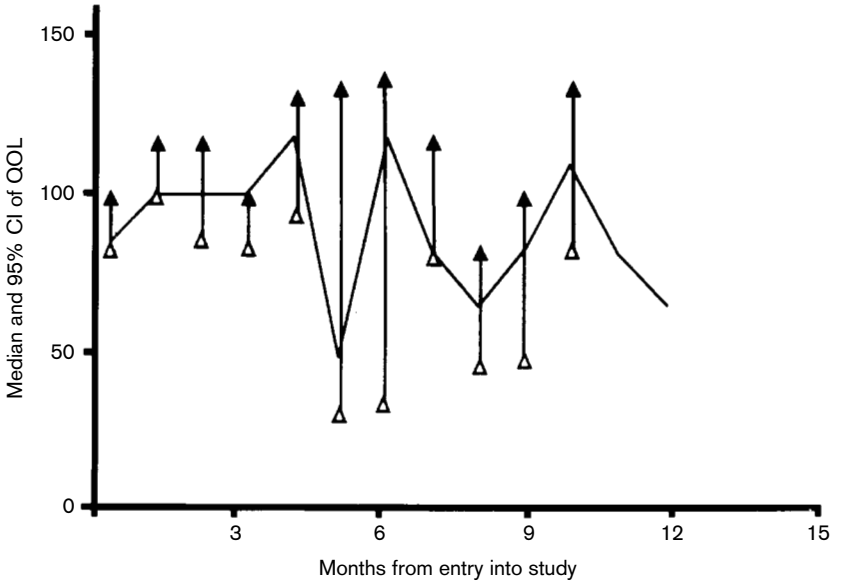

Figure 4. Graph of the median FLIC score over time.

trioid cell type and the pelvic site of the tumor might be favorable to megestrol acetate treatment. However, the ER and PgR status had not been evaluated in our study population. The median survival of our study population was 5.8 months, which is quite short. This might be due to the poor prognostic characteristics (advanced stage, large extent of disease, poor performance status and heavy pretreatment) of our study population. However, median survival was clearly longer in the responder group than in the non-responder group, as was the progression-free survival. Interestingly, one of the CR patients is still alive without recurrence of the disease during a 3-year period. In this study, the megestrol acetate serum levels were not measured in all patients.

The major side effects of high-dose megestrol acetate in this trial were increased appetite and weight gain, which were acceptable to the vast majority of patients. In fact, these side effects were considered beneficial by some patients; only four of them had a weight gain of more than 20%. The serious complication of thromboembolism did not occur in any patient with this dose level of megestrol acetate. Megestrol acetate was previously shown to have cortisol-like effects and there were also case reports of adrenal suppression in AIDS patients treated with megestrol acetate for cachexia.[27–29] Naing *et al*. demonstrated biochemical hypoadrenalism in patients on megestral acetate, but not symptomatic.[30] In our series, we did not have any patient with clinical hypoadrenalism. Mild alopecia in our series did not trouble the patient.

There has been increasing interest in the concept of the QOL of cancer patients. Measurement of QOL has recently been proposed as a component of clinical trials research.[31–34] The FLIC has been used widely in clinical trials, is reasonably easy to complete and has shown sensitivity to changes over time.[35–39] In our study population whose Zubrod performance status was rather poor (more than 50% had Zubrod performance status of 2), the median FLIC score was fair (around 90) and quite constant over time.

We conclude that megestrol acetate has modest but definite activity in patients with platinum-refractory EOC, particularly in a small subset of the endometrioid subtype with limited disease in the pelvis. Only minimal toxicity was observed and the patients had a fair QOL score (FLIC) during the treatment.

Acknowledgments

We would like to express our sincere gratitude to Dr Somsak Tangtrakul, Dr Sunchai Bullangpoti and Dr Nathpong Israngura Na Ayudhya.

References

1. Seewaldt VL, Greer BE, Cain JM, *et al*. Paclitaxel (taxol) treatment for refractory ovarian cancer: phase II clinical trial. *Am J Obstet Gynecol* 1994; **170**: 1666–70.
2. Neijt JP, Ten Bokkel Huinink WW, Van der Berg ME. Long-term survival in ovarian cancer: mature data from the Netherlands Joint Study Group for Ovarian Cancer. *Eur J Cancer* 1991; **27**: 1367–72.
3. Schwartz PE, LiVolsi VA, Hildreth N, *et al*. Estrogen receptors in ovarian epithelial carcinoma. *Obstet Gynecol* 1982; **59**: 229–38.
4. Holt JA, Caputo TA, Kelly KM, *et al*. Estrogen and progestin binding in cytosols of ovarian adenocarcinomas. *Obstet Gynecol* 1979; **53**: 50–8.
5. Janne O, Kauppila A, Syrjala P, *et al*. Comparison of cytosol estrogen and progestin receptor status in malignant and benign tumors and tumor-like lesions of human ovary. *Int J Cancer* 1980; **25**: 175–9.
6. Bergqvist A, Kullander S, Thorell J. A study of estrogen and progesterone cytosol receptor concentration in benign and malignant ovarian tumors and a review of malignant ovarian tumors treated with medroxyprogesterone acetate. *Acta Obstet Gynecol* 1981; **101**(suppl): 75–81.
7. Creasman WT, Sasso RA, Weed JC, *et al*. Ovarian carcinoma: histologic and clinical correlation of cytoplasmic estrogen and progesterone binding. *Gynecol Oncol* 1981; **12**: 319–27.
8. Galli MC, De Giovanni C, Nicoletti G, *et al*. The occurrence of multiple steroid hormone receptors in disease-free and neoplastic human ovary. *Cancer* 1981; **47**: 1297–320.
9. Hahnel R, Kelsall GRH, Martin JD, *et al*. Estrogen and progesterone receptors in tumors of the human ovary. *Gynecol Oncol* 1982; **13**: 145–51.
10. Kauppila A, Vierikko P, Kivinen S, *et al*. Clinical significance of estrogen and progestin receptors in ovarian cancer. *Obstet Gynecol* 1983; **6**: 320–6.
11. Ford LC, Berek JS, Lagasse LD, *et al*. Estrogen and progesterone receptors in ovarian neoplasms. *Gynecol Oncol* 1983; **15**: 299–304.
12. Spoona J, Gitsch E, Salzer H, *et al*. Estrogen and gestagen-receptors in ovarian carcinoma. *Gynecol Obstet Invest* 1983; **16**: 189–98.
13. Sutton GP, Senior MB, Strauss JF, *et al*. Estrogen and progesterone receptors in epithelial ovarian malignancies. *Gynecol Oncol* 1986; **23**: 176–82.
14. Bizzi A, Codegoni AM, Landoni F, *et al*. Steroid receptors in epithelial ovarian carcinoma: relation to clinical parameters and survival. *Cancer Res* 1988; **48**: 6222–6.
15. Runge HM, Teufel G, Neulen J, *et al*. *In vitro* responsiveness of ovarian epithelial carcinomas to endocrine therapy. *Cancer Chemother Pharmacol* 1986; **16**: 58–63.
16. Geisler HE. The use of high-dose megestrol acetate in the treatment of ovarian adenocarcinoma. *Semin Oncol* 1985; **12**: 20–2.
17. Sikic BI, Scudder SA, Ballon SC, *et al*. High-dose megestrol acetate therapy of ovarian carcinoma: a phase II study by the Northern California Oncology Group. *Semin Oncol* 1986; **13**: 26–32.
18. Schipper H, Clinch J, McMurrary A, *et al*. Measuring the quality of life of cancer patients: the functional living index—cancer: development and validation. *J Clin Oncol* 1984; **2**: 472–83.

19. *WHO handbook for reporting results of cancer treatment 48*. Geneva: WHO 1979.
20. McGuire WP, Rowinsky EK, Rosenshein NB, *et al*. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989; **111**: 273–9.
21. Markman M, Reichman B, Hakes T. Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. *J Clin Oncol* 1991; **9**: 1801–5.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**: 457–81.
23. Weirnik PH, Greenwald ES, Ball H, *et al*. High-dose megestrol acetate in the treatment of patient with ovarian cancer who have undergone previous treatment: Eastern Cooperative Oncology Group Study PD 884. *Am J Clin Oncol* 1998; **21**: 565–7.
24. Ahlgren ID, Ellison NM, Gottlieb RJ, *et al*. Hormonal palliation of chemoresistant ovarian cancer: three consecutive phase II trials of the Mid-Atlantic Oncology Program. *J Clin Oncol* 1993; **11**: 1957–68.
25. Veenhof CH, van der Gurg ME, Nooy M, *et al*. Phase II study of high-dose megestrol acetate in patients with advanced ovarian carcinoma. *Eur J Cancer* 1994; **304**: 697–8.
26. Ford LC, Berek JS, Lagasee LD. Estrogen and progesterone receptors in ovarian neoplasms. *Gynecol Oncol* 1983; **115**: 229–304.
27. Leinung MC, Liporace R, Miller CH. Induction of adrenal suppression by megestrol acetate in patients with AIDS. *Ann Intern Med* 1997; **157**: 1008–11.
28. Subramanian S, Goker H, Kanji A, *et al*. Clinical adrenal insufficiency in patients receiving megestrol therapy. *Arch Intern Med* 1997; **157**: 1008–11.
29. Stoffner SS, Krakauer JC. Induction of adrenal suppression by megestrol acetate [Letter]. *Ann Intern Med* 1996; **124**: 613–4.
30. Naing KK, Dewar JA, Leese GP. Megestrol acetate therapy and secondary adrenal suppression. *Cancer* 1999; **86**: 1044–9.
31. Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. *Lancet* 1976; **i**: 899–901.
32. Sugarbaker PH, Barofsky I, Rosenberg SA, Gianola FJ. Quality of life asessment of patients in extremity sarcoma clinical trials. *Surgery* 1982; **91**: 17–23.
33. Bell DR, Tannock IF, Boyd NF. Quality of life measurement in breast cancer patients. *Br J Cancer* 1985; **52**: 577–80.
34. Johnson JR, Temple R. Food and drug administration requirements for approval of new anticancer drugs. *Cancer Treat Rep* 1985; **69**: 1155–7.
35. Kornblith AB, Hollis DR, Zuckerman E, *et al*. Effect of megestrol acetate on quality of life in a dose–response trial in women with advanced breast cancer. *J Clin Oncol* 1993; **11**: 2081–9.
36. Andrykowski MA, Altmaier EM, Barnett RL, *et al*. The quality of life in adult survivors of allogeneic bone marrow transplantation: correlates and comparison with matched renal transplant recipients. *Transplantation* 1990; **50**: 399–406.
37. Peters WP, Ross M, Vredenburgh JJ, *et al*. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993; **11**: 1132–43.
38. Cassileth BR, Soloway MS, Vogelzang NJ, *et al*. Quality of life and psychosocial status in stage D prostate cancer. Zoladex Prostate Cancer Study Group. *Qual Life Res* 1992; **1**: 323–9.
39. Finkelstein DM, Cassileth BR, Bonomi PD, *et al*. A pilot study of the Functional Living Index—Cancer (FLIC) scale for the assessment of quality of life for metastatic lung cancer patients. *Am J Clin Oncol (CCT)* 1988; **11**: 630–3.

(Received 5 April 2001; revised form accepted 5 July 2001)