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COMPARISON OF THE EFFECTS OF HIGH DOSE ESTRAMUSTINE PHOSPHATE AND MITOMYCIN C ON THE TIME TO PROGRESSION AND LENGTH OF SURVIVAL OF PATIENTS WITH PROGRESSIVE, ADVANCED ENDOCRINE-INDEPENDENT PROSTATIC CANCER: AN INTERIM ANALYSIS OF EORTC-GU GROUP STUDY NO. 30865

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Summary—Patients with hormone escaped advanced progressive prostate cancer were randomized either to receive either high-dose Estramustine phosphate orally or Mitomycin C by i.v. injection every 6 weeks until signs of progression or death supervened. Patients on both arms progressed rapidly, with a median time to progression of 5 months and a median length of survival of only 10 months. Toxicity was very considerable in both arms.

INTRODUCTION

Patients presenting with metastatic prostatic carcinoma will usually respond to standard endocrine treatment by orchidectomy, LHRH agonist or other anti-androgen therapy. Of the 80% who initially respond, 50% relapse within 3 years and there has, to date, been no very satisfactory way of limiting their disease thereafter, clinicians main efforts being directed towards symptom palliation. Following a series of Phase II investigations carried out by the EORTC-GU Group, Mitomycin was found to be moderately effective in the treatment of patients who had relapsed following primary hormonal therapy. In a previous study of 27 patients with metastatic disease [1], a partial response rate of 28% was found where Mitomycin was used in a dose of 15 mg/m^2 every 6 weeks. Estramustine phosphate is a combination oestrogen/nitrogen mustard which has been shown to be effective in both primary and secondary therapy in advanced prostatic cancer. Recently, in high doses, i.e. >560 mg/day [2, 3], it has been shown to exert a direct cytotoxic action which was not apparent at lower dosages. Since there were a substantial number of patients relapsing on primary hormonal therapy who initially presented with metastatic disease, the EORTC-GU Group in 1986 felt that it was appropriate to investigate these two agents in a randomized, prospective, multicentric Phase III study.

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MATERIALS AND METHODS

One hundred and seventy-seven patients were randomized between the two arms of a Phase III prospective multicentric study between September 1986 and April 1989. All patients had proven progression of their advanced prostatic cancer, the majority progressing both in their metastases and primary tumour. Previous treatments were mainly hormonal, although a few patients had received local irradiation, either to the primary tumour or pelvic lymph nodes, and a few had undergone palliative irradiation to painful metastases or had received steroid therapy. At the time of this interim analysis 143 patients had gone off-study for progression, including death due to malignant disease or toxicity; 110 of these have been fully evaluated and form the basis for this report. In March 1990 the status of evaluation was as summarized in Table 1. The patients randomized in this study all came from institutions with members in the EORTC-GU Group. Their affiliations are shown in Table 2.

The characteristics of the 152 eligible patients are shown in Table 3, where it can be seen that

Table 1. Status of evaluation by the study co-ordinator (@ March 90)

No. of patients randomized	177
No. of patients off-study	143
No. of patients evaluated	110
Ineligible	12 (7%)
Partially evaluable	7 (4%)
Fully evaluable	91

a substantial number of patients had other chronic diseases and the majority of patients had pain varying from mild to intractable, i.e. requiring regular narcotic analgesia.

The majority had a performance status of 1 on the ECOG scale, a few had a worse performance status. All patients had been treated previously with hormonal manipulation and some patients had undergone as many as five different therapies prior to admission to the study.

The TN and G categories of the patients follow the usual pattern seen in other similar studies on metastatic prostatic cancer [4]. The majority had advanced T stage and the G category was usually G2–G3 (Table 4). The majority of the patients had not undergone any lymph node staging but a few had at the time of radical prostatectomy. 65% of the patients had progressed in their metastatic disease only, but 25% had both metastatic and local progression at the time of entry into the study.

THERAPEUTIC REGIME

Mitomycin C was administered by i.v. injection into a slowly running saline drip every 6 weeks. This was performed as a day case and no patients had to be admitted for the infusion. Estramustine phosphate was given in tablet form by mouth and the initial dose was 560 mg, i.e. 4 tablets/day. Attempts was made to escalate the dose to 700 mg after 2 weeks but only half of the patients were able to tolerate this high dose, principally due to gastro-intesinal side effects; 10% of patients who did manage to escalate the dose of Estracyt returned to the original dose for the same reason (Table 5).

Table 2. Eligible patients by institution

Oslo	29
Offenbach	19
P. R., Hull	15
AMC, Amsterdam	13
VUB, Brussels	9
HOP, Cochin, Paris	8
AVL, Amsterdam	7
Varese	7
Bichat, Paris	7
CHU, Liège	6
St Luc, Brussels	6
Radboud, Nijmegen	5
Ramaz, Carpi Modena	4
Newcastle	3
München	3
Castleford	3
AZ, Gent	3
St Jozef, Oostende	3
Curry Cabral, Lisbon	3
W. A., Den Bosch	2
GZG, Hertogenbosch	2
AZ, Utrecht	1
OLVG, Amsterdam	1
AZ, Groningen	1
Santa Maria, Lisbon	1
York	1
Zuiderz, Rotterdam	1
Erasmus	1
AZ, Maastrict	1
Total	165

Table 3. Patient characteristics (152 patients)

WHO performance status	
0	18 (12%)
1	74 (49%)
2	40 (26%)
3	20 (13%)
Chronic diseases	
Cardiovascular	75 (49%)
Respiratory	15 (10%)
Musculo-skeletal	5 (3%)
Other	14 (9%)
Pain	
None	29 (19%)
Mild	36 (24%)
Moderate	41 (27%)
Severe	11 (7%)
Intractable	35 (23%)

TOXICITY OF TREATMENT

The toxicity experienced by this group of patients has been disappointingly severe. Many patients, a total of 28% who have been evaluated so far, have stopped treatment for this reason. In the Estracyt arm, 56% of them stopped within the first 6 weeks of treatment; in those patients receiving Mitomycin C some stopped after only 1 injection and some after as many as 8. The toxicity responsible for patients stopping treatment is summarized in Table 6.

Table 4. Disease characteristics (152 patients)

T category on study	
0	1 (1%)
1	4 (3%)
2	13 (9%)
3	45 (30%)
4	56 (37%)
X	32 (21%)
N category	
0	27 (18%)
1	2 (1%)
2	8 (5%)
3	6 (4%)
4	19 (13%)
X	90 (59%)
Histology G category	
1	16 (10%)
2	66 (43%)
3	60 (40%)
X	10 (7%)

Table 5. Estracyt dose escalation to 700 mg/day

No	27 (39%)
Yes	35 (51%)
Return to 560 mg/day	7 (10%)
Total	69

Table 6. Stopped treatment due to side effects

	Estracyt	Mitomycin C
Haematological	0	12 (16)
Gastro-intestinal	18 (22)	2 (3)
Cardiovascular	6 (7)	0
Painful gynecomastia	3 (4)	0
General malaise	1 (1)	0
Dyspnoea	0	1 (1)
Massive pneumonia	0	1 (1)
Total	28/82 34%	16/76 21%
Time at which stopped	56% within the first 6 weeks	Ranging from 1 to 8 injections (i.e. 6–48 weeks)

It can be seen that the principal side effects of treatment with Estracyt were gastro-intestinal, while those of Mitomycin C were haematological. The haematological side effects of Mitomycin C generally consisted of low white counts, i.e. $<4.0 \times 10^9/l$ and platelets $<100{,}000$. If the haemoglobin fell to 9.0 g/dl a bone marrow aspiration was performed and in at least one case Mitomycin C marrow toxicity resulted in the death of a patient. The gastro-intestinal side effects of Estracyt therapy were mainly those of nausea, anorexia and vomiting

Table 7. Reason off study (%)

	Estracyt	Mitomycin C	Total
Toxicity	25 (37)	15 (24)	40 (31)
Progression	32 (47)	36 (57)	68 (52)
Other	11 (16)	12 (19)	23 (17)
Off/total	68/84 (81)	63/81 (78)	131/165

Table 8. Cause of death

	Estracyt	Mitomycin C	Total
Malig. disease	41 (85)	33 (73)	74 (80)
Toxicity	0 (0)	1 (2)	1 (1)
Infection	0 (0)	2 (4)	2 (2)
Cardiovascular	5 (10)	6 (13)	11 (12)
Other/unknown	2 (4)	3 (7)	5 (5)
Total	48/84 (57)	45/81 (55)	93/165

often associated with considerable loss of weight. Table 7 shows the reasons for patients going off study, wherein it can be seen that the majority went off-study because of progression although 30% have gone off-study out of the first 165 patients because of toxicity. The difference between Estracyt and Mitomycin C is not statistically significant in this respect.

RESULTS

In this study a large number of patients have already died. Of the patients presently eligible, 93 of 165 have died, the causes of death are summarized in Table 8.

While the majority have died of malignant disease, cardiovascular and other causes have

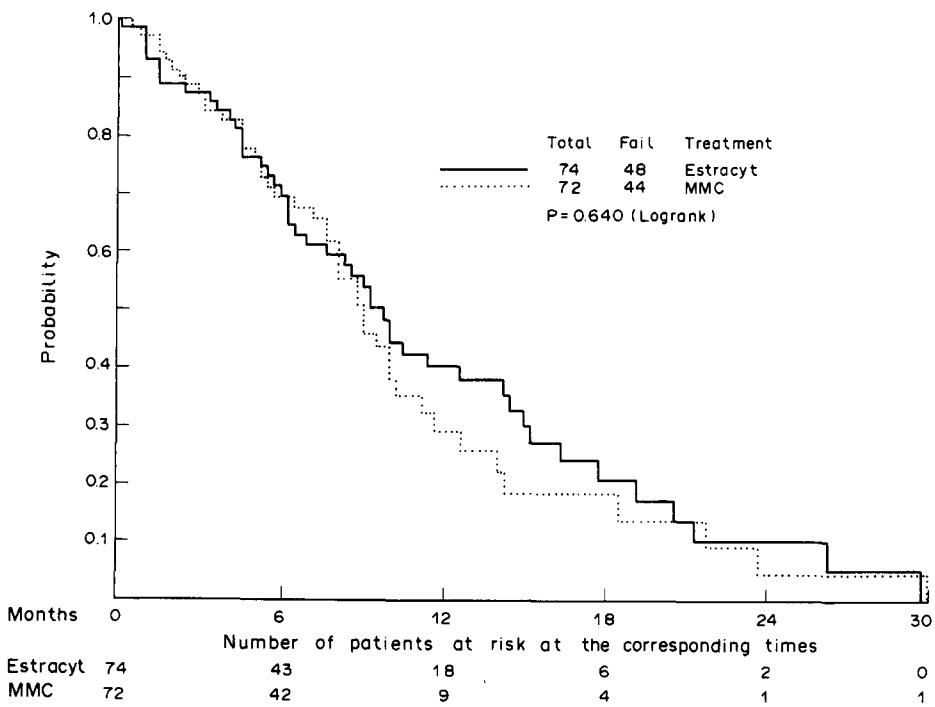

Fig. 1. Time to progression.

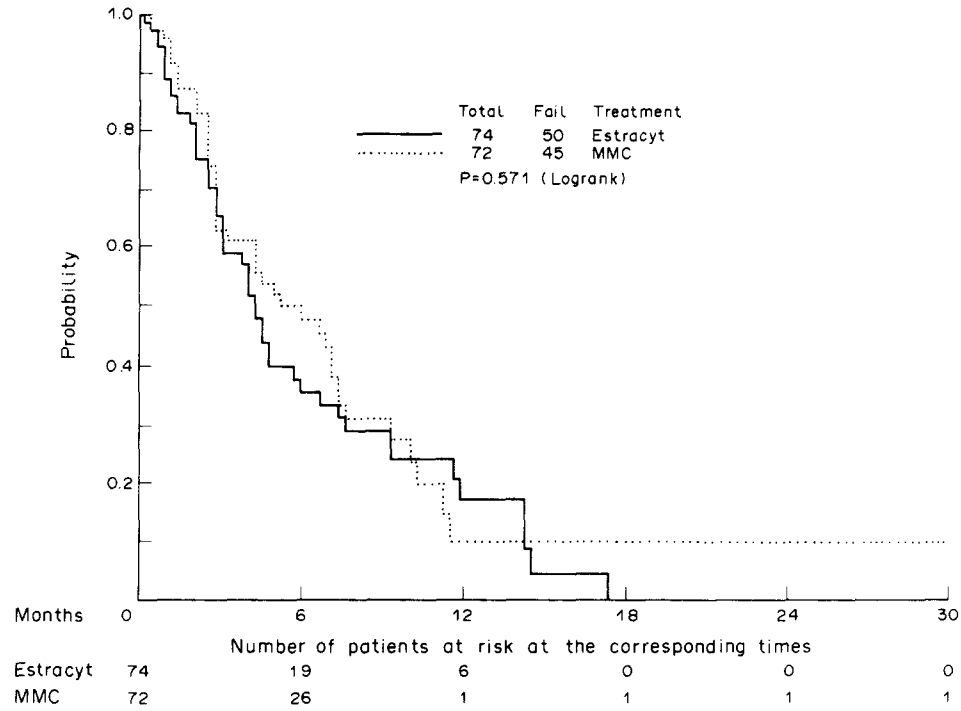

Fig. 2. Duration of survival.

contributed significantly that there has been one toxic death due to bone marrow suppression.

The mean time of progression in this study is identical for both the Estracyt and Mitomycin C arms and is summarized in Fig. 1. The median time to progression is 5 months.

Survival after the onset of this treatment is very short-lived. The median time to death is 10 months and there is no difference between Estracyt or Mitomycin C in this respect (Fig. 2).

DISCUSSION

The best way to manage hormone escaped cancer still remains an enigma. There is no doubt that the hormone-insensitive or hormone-resistant cells [5, 6] are responsible for a patient's death from prostatic cancer. No particularly effective single chemotherapeutic agent has yet been discovered and while the two agents used in this study are probably amongst the most effective, their ability to prolong survival and lengthen the time to progression has proved most disappointing. What is of equal importance in this group of patients is the serious toxicity which patients in both arms of the study have suffered. It is quite clear that with this degree of toxicity and poor therapeutic response neither regime employed in this study is of proven benefit in this group of patients. When compared to simple palliation with analgesics, hemibody irradiation or local irradiation, the length of survival does not appear to have been significantly prolonged [7]. It is quite clear that in this group of patients neither Mitomycin C nor Estracyt in the dosage used in this study can be recommended for the treatment of hormone escaped advanced progressive prostatic cancer.

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