Shrinkage of the mass (≥68.4%/70% in size /≥90% in area)

Code	Author	Year	Shrinkage ≥90% n	Nec(%)	Ter(%)	Can(%)	Shrinkage <90% n	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	34	71	23	6	42	64	33	2
102	Stomper *et al.* [15]*	1985	10	70	10	20	21	57	29	14
102	Donohue *et al.* [11]+	1987	24	71	25	4	56	32	48	20
102	Sagalowsky *et al.* [16]+	1990	7	40	40	20	10	40	30	30
102	Mulders *et al.* [26]	1990	12	83	17	0	22	45	41	14
102	Toner *et al.* [3]	1990	25	72	16	12	61	39	44	16
102	Steyerberg *et al.* [8]	1993	11	73	9	18	64	36	45	19
312	Pizzocaro *et al.* [24]	1985	13	69	15	15	21	24	38	38
Total			134	71	19	11	297	41	41	17

*n indicates in this study the number of residual masses, not the number of resections
+A reduction over 90% in volume was used as a criterium for 'large reduction in size'.

Type of resection

Code	Author	Year	Lung resection n	Nec(%)	Ter(%)	Can(%)	Abdominal resection n	Nec(%)	Ter(%)	Can(%)
302	Bracken *et al.* [27]	1983	15	33	27	40	22	36	31	32
302	Mulders *et al.* [26]	1990	8	63	25	13	34	59	32	9
302	Toner *et al.* [3]	1990	39	64	26	10	122	46	40	14
302	Steyerberg *et al.* [8]	1993	20	60	30	10	75	41	40	19
312	Fosså *et al.* [12]	1989	9	56	33	11	92	51	47	12
Total			91	57	27	15	345	47	38	15

Pergamon

European Journal of Cancer Vol. 30A, No. 9, pp. 1239–1244, 1994

0959-8049/94 $7.00+0.00

0959-8049(94)00239-8

Long-term Results of Two VAB-like Regimens (Vinblastine + Actinomycin-D + Bleomycin + Cyclophosphamide + Cisplatin) in Malignant Germ Cell Tumours of the Ovary

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21 patients with malignant germ cell tumours of the ovary were treated with two chemotherapy regimens including vinblastine, actinomycin-D, bleomycin, cyclophosphamide and cisplatin. Chemotherapy was delivered as primary postoperative therapy in 15 patients and for recurrent disease in 6 patients. 3 of 4 patients with pure dysgerminomas and 10 of 17 patients with non-dysgerminomatous tumours are alive without evidence of disease. The overall progression-free survival is 62% (95% confidence interval 45–77) with a median follow-up of 7 years. Two toxic deaths were observed. Less toxicity and better efficacy favour etoposide- and cisplatin-based regimens as standard chemotherapy for germ cell tumours of the ovary.

Keywords: germ cell tumours, ovary, chemotherapy
Eur J Cancer, Vol. 30A, No. 9, pp. 1239–1244, 1994

INTRODUCTION

MALIGNANT OVARIAN germ cell tumours account for <5% of all ovarian neoplasms, and their incidence is approximately one tenth that of testicular cancer [1]. The pathological classification mainly distinguishes pure dysgerminoma, the female equivalent of seminoma, and tumours other than pure dysgerminoma, the so-called non-seminomatous germ cell tumours (NSGCT) [2].

Dysgerminoma is radiosensitive, and radiotherapy has been used in the postoperative treatment of patients with primary disease as well as in patients with recurrent disease. Several

studies have documented a radiocurability of 60 to 100% [3–5]. However, abdominopelvic radiotherapy, even with the rather low doses employed in dysgerminoma, is associated with a high incidence of ovarian failure and sterility. Chemotherapy has been developed as an alternative treatment that could produce equivalent results in low stages and superior survival rates in metastatic disease, while preserving the reproductive capacities [6].

The prognosis for patients with NSGCT of the ovary was dismal until the advent of combination chemotherapy. All patients with advanced disease died. Only 5–20% of patients with stage I disease survived after treatment with surgery alone [7, 8]. The adjunct of postoperative treatment with radioisotopes, external radiation therapy or single-agent chemotherapy failed to improve these highly disappointing results [9].

The first effective progress were reported with the VAC regimen, a combination of vincristine, actinomycin-D and cyclophosphamide. Two decades of experience with VAC revealed a high proportion of cure in stage I disease (85%), but the sustained remission rate was less than 50% in patients with metastatic tumours [10]. The successful introduction of cisplatin into clinical trials for male germ cell cancer prompted investigators to use cisplatin-based regimens in patients with ovarian germ cell tumours. In 1974, the combination of cisplatin, vinblastin and bleomycin (PVB) was studied in patients with testicular cancer, and the initial publication remains a landmark study in modern oncology [11]. The PVB regimen was applied to non-dysgerminomatous germ cell tumours of the ovary, and results were superior to those obtained with the VAC combination in patients with advanced diseases. However, the rarity of the disease precluded randomised trials, and up to 40% of patients failed the PVB regimen [12, 13]. Other investigators developed, in male germ cell tumours, a series of combination regimens named VAB, where cisplatin was mainly associated with vinblastin, bleomycin, actinomycin-D and cyclophosphamide [14–16].

From 1978 to 1990, we studied, at the Institut Gustave Roussy, two successive VAB-like chemotherapy regimens in ovarian germ cell cancers. The present study describes the long-term results obtained with such combinations in 21 patients.

PATIENTS AND METHODS

From August 1978 to October 1990, 21 patients with malignant germ cell tumours of the ovary were included in two successive VAB-like regimens. The age of the patients ranged from 15 to 33 years (median 22). All patients underwent initial surgery. The initial operative procedure consisted of biopsy alone in 1 patient, unilateral salpingo-oophorectomy in 9 patients, unilateral salpingo-oophorectomy with total hysterectomy and/or omentectomy in 6 patients, and bilateral salpingo-oophorectomy with total hysterectomy and/or omentectomy in 4 patients. Only 1 patient underwent bilateral salpingo-oophorectomy alone. Histological materials were reviewed at Institut Gustave-Roussy, and classified according to World Health Organization criteria [2]. The tumours were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system.

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Revised 20 Apr. 1994; accepted 7 June 1994.

From August 1978 to March 1985, 12 patients were treated with the AVAB regimen which included actinomycin-D 0.1 mg/kg/day intravenously (i.v.) and cyclophosphamide 300 mg/m^2/day i.v. on days 1 to 5, vincristine 2 mg i.v. on day 28, doxorubicin 60 mg/m^2 i.v. on day 28, bleomycin 20 mg/day on days 28 to 30, and cisplatin 100 mg/m^2 on day 30. 4 patients also received chlorambucil 4 mg/m^2 day by mouth (2 patients) or methotrexate 15 mg/m^2/day intramusculary (2 patients) for 7 days every month. This regimen was repeated at 4-week intervals. From November 1982 to October 1990, 9 patients were treated with the VAB-6 regimen which included actinomycin-D 1 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. and vinblastine 4 mg/m^2 i.v. on day 1, bleomycin 30 mg i.v. push on day 1 and 20 mg/m^2/day in continuous infusion days 1 to 3, cisplatin 120 mg/m^2 i.v. on day 4. Each cycle was repeated every 4 weeks.

Prior to each cycle of chemotherapy, patients underwent a complete blood count, platelet count, chemical survey, serum tumour markers analysis and chest radiographs. Therapy was delayed when necessary until the neutrophil and platelet counts were superior to 1000/mm^3 and 100000/mm^3, respectively. There were no dose modifications due to haematological toxicity. Bleomycin was withdrawn in patients with grade IV mucositis or clinical pulmonary toxicity. No pulmonary function tests were routinely performed. Second-look laparotomy consisting of excision of all suspicious-appearing areas, cytological washings and random biopsies was performed in suitable cases. Chemotherapy was discontinued in patients who had no evidence of disease at laparotomy.

Response criteria were as follows: clinical complete response, disappearance of all evidence of tumour including normalisation of human chorionic gonadotrophin (HCG) and α-fetoprotein (AFP) for at least 1 month; partial response, more than 50% reduction in the sum of the products of the largest diameter and its perpendicular for measurable lesions and more than 90% reduction of elevated tumour markers for at least 1 month with no evidence of progression in any site. Patients with complete excision of mature teratoma and/or fibrosis and/or necrosis at second-look laparotomy were considered as pathological complete response. Patients with complete excision of residual active disease were considered as surgical complete responses.

After treatment, patients were followed every 2 months during 1 year and at gradually increasing intervals thereafter. Progression-free survival was measured from the end of treatment to the time of death or until 1 June 1993, whichever came first.

RESULTS

VAB protocols as primary postoperative chemotherapy

15 patients received VAB regimens as primary postoperative therapy, of whom 8 were treated with AVAB and 7 with VAB-6 combinations. Patients' characteristics are shown in Table 1.

6 patients (1 with dysgerminoma and 5 with non-dysgerminomatous tumours) had no macroscopic residual disease after initial surgery (patients 1–6). 5 patients are alive without evidence of disease 55 to 122 months after time of diagnosis. 2 of them (patients 2 and 4) underwent a second-look laparotomy which revealed no residual disease. Patient 6 failed with the VAB-6 protocol but is now without evidence of disease after a salvage treatment with VIP regimen (etoposide + ifosfamide + cisplatin) and subsequent second-look surgery. Patient 1 experienced an abdominal peritoneal relapse after the third cycle of AVAB combination. She was switched to a combination of high-dose cisplatin, vinblastine, bleomycin and etoposide (PVeBV

Table 1. Characteristics of the 15 patients who received VAB protocols as primary postoperative therapy

Patients no.	Age (years)	Initial surgery	FIGO stage	Residual disease	Histology	AFP/HCG before chemotherapy	Chemotherapy	Second-look laparotomy	Response	Status	Survival (months)
1	17	BS0+TH+0	IC	No	EC+EST	820/4	AVAB × 3	EST	PD	DOD	12
2	16	RS0	IC	No	IT	315/4	AVAB × 6	Negative	pCR	NED	122+
3	26	BS0+TH	IC	No	EST	ND/ND	AVAB × 4	ND	cCR	NED	75+
4	23	RS0+TH	IA	No	IT	2/4	VAB × 4	Negative	pCR	NED	65+
5	25	BS0	IC	No	D	2/4	VAB × 4	ND	cCR	NED	60+
6	26	LS0	IC	No	MT+IT	3/4	VAB × 2	ND	PD	NED	55+
7	33	RS0+TH	IIIB	<2 cm	IT+EST	600/4	AVAB × 6	Negative	pCR	NED	156+
8	16	BS0+TH	IIIC	<2 cm	IT	230/4	AVAB × 2	MT	pCR	NED	76+
9	25	RS0+0	IIIB	<2 cm	IT	3/4	VAB × 4	MT	pCR	NED	35+
10	26	RS0+0	IIIB	<2 cm	IT	4/4	VAB × 3	MT	pCR	NED	24+
11	23	RS0	IIIC	>2 cm	EST	40000/4	AVAB × 3	ND	cCR	DOT	9
12	27	LS0	IV	>2 cm	IT+EST	2050/4	AVAB × 3	ND	PD	DOD	11
13	17	Biopsy	IIIC	>2 cm	D+EST	17400/4	AVAB × 5	EST	sCR	DOD	11
14	15	BS0+TH	IIIC	>2 cm	IT	3000/4	VAB × 2	ND	PD	DOD	10
15	16	LS0+0	IIIC	>2 cm	D	2/4	VAB × 4	Negative	pCR	NED	56+

BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; TH, total hysterectomy; O, omentectomy; D, dysgerminoma; IT, immature teratoma; MT, mature teratoma; EC, embryonal carcinoma; EST, endodermal sinus tumour; VAB, VAB-6 regimen; cCR, clinical complete response; pCR, pathological complete response; sCR, surgical complete response; PD, progressive disease; ND, not done; DOD, dead of disease; DOT, dead of toxicity; NED, no evidence of disease.

regimen), but failed to respond and eventually died 12 months after diagnosis.

All 4 patients who had non-dysgerminomatous tumours with minimal residual disease after primary surgery are alive without evidence of disease 24 to 156 months after diagnosis (patients 7–10). 3 of them had excision of mature teratoma lesions at second-look laparotomy.

Among 5 patients (patients 11–15) with bulky residual disease after primary surgery, patients 12 and 14 primarily failed to respond and died of disease. Patient 13 was considered as a surgical complete responder after second-look laparotomy. However, she relapsed 3 months later and ultimately died of disease. Patient 11 died of liver toxicity 9 months after diagnosis, despite complete clinical response with AVAB combination including methotrexate (total dose 1550 mg). The unique patient with pure dysgerminoma obtained a pathological complete response after VAB-6 therapy and is alive without evidence of disease 56 months after diagnosis.

VAB protocols for recurrent disease

6 patients relapsed after initial therapy which consisted of surgery alone (5 patients) or surgery plus radiotherapy (1 patient). Their characteristics are shown in Table 2. For 1 of them (patient 1), surgery was obviously incomplete since relapse occurred only 3 months after diagnosis. Patient 5 had pure dysgerminoma, and received postoperative adjuvant radiotherapy to ipsilateral hemipelvis and para-aortic lymph nodes. Relapses occurred in the pelvis alone in 2 patients (patients 1 and 5), in the pelvis and omentum in 1 patient (patient 4), in the omentum alone in 1 patient (patient 3), in the spleen and liver in 1 patient (patient 2), and in para-aortic and left supra-clavicular lymph nodes in 1 patient (patient 6). No surgery was performed at relapse before the onset of VAB chemotherapy. 5 patients achieved clinical or pathological responses after VAB regimens, of whom 3 are continuously without evidence of disease 60–180 months from time of diagnosis. Patient 2 died of renal toxicity, despite clinical complete response. Patient 5 experienced a huge

Table 2. Characteristics of the 6 relapsing patients who received VAB protocols

Patients no.	Age (years)	Initial treatment	Histology	Interval from diagnosis to chemotherapy (months)	AFP/HCG before chemotherapy	Chemotherapy	Response	Status	Survival (months)
1	18	RS0	EST	3	27500/4	AVAB × 5	cCR	NED	180+
2	20	LS0	IT	11	33/4	AVAB × 2	cCR	DOT	14
3	23	LS0	IT	6	3/4	AVAB × 3	pCR	NED	60+
4	20	RS0+0	IT+EC	6	34900/4	AVAB × 2	PD	DOD	9
5	24	RS0+RT	D	11	3/4	VAB × 5	cCR	DOD	25
6	28	LS0	D	20	3/4	VAB × 3	cCR	NED	65+

For most abbreviations, see Table 1. RT, radiotherapy; D, dysgerminoma; EC, embryonal carcinoma.

peritoneal relapse 8 months later and eventually died. Only 1 patient (patient 4) primarily failed to respond and rapidly died 9 months after diagnosis.

Serum tumour markers

We have developed at our Institute a prognostic model based on a multivariate analysis in patients with NSGCT of the testis [17]. In this model, the tumour markers correlate strongly with tumour burden and prognosis. A combination of serum HCG and AFP levels gives a probability of complete response, and allows the definition of prognostic groups. Patients are assigned to the good prognosis group when the probability of complete response is equal to or greater than 70%. Patients with a less than 70% complete response probability are allocated to the poor prognosis group.

In the present report, only 1 patient had no available serum tumour markers before therapy in the NSGCT group. According to our prognostic model, 10 patients would have been assigned to the good prognosis group, while 6 patients would have been allocated to the poor risk group. In the former group, only 1 patient died of progressive disease and 1 patient experienced fatal renal toxicity, despite complete clinical response. In the poor prognosis group, only 1 is alive without evidence of disease and 1 patient died of liver toxicity in a complete response setting.

Toxicity

Forty-four cycles of AVAB in 12 patients and 31 cycles of VAB-6 in 9 patients were delivered. The mean number of cycles per patient was 3.7 and 3.4, respectively. The toxicities are reported in Table 3 according to the worst side-effect encountered by each patient. Two toxic deaths were noted with the AVAB regimen. One patient died in a context of acute renal failure without evidence of sepsis, and the other was treated with methotrexate and experienced acute hepatic failure after the third cycle of chemotherapy. These 2 patients were considered to be in clinical complete response when organ failures occurred. The overall haematological and mucous toxicities were greater with the AVAB protocol as compared to the VAB-6 regimen. Bleomycin was discontinued in 3 patients treated with the AVAB protocol and in 1 patient treated with the VAB-6 regimen because of grade 3–4 mucositis. Reversible alopecia was noted in all patients. No clinical pulmonary toxicity was detected in either protocol. 8 patients had conservative surgery with unilateral salpingo-oophorectomy and are alive without evidence of disease. Amenorrhoea and oligomemorrhoea developed during chemotherapy administration. After completion of therapy, all but one resumed normal menstrual function. Only one child was delivered from 3 patients who attempted pregnancy.

13 of 21 patients are alive without evidence of disease after a median follow-up of 7 years. The overall progression free-survival is 62% [95% confidence interval (CI) 45–77].

Table 3. Toxicity of the VAB protocols according to the worst side-effect encountered by each patient (WHO scale)

	AVAB						VAB-6				
Toxicities	0	1	2	3	4	5	0	1	2	3	4
Haematological											
White blood count	0	0	2	2	8	0	0	1	2	3	3
Platelets	3	3	1	2	3	0	5	1	2	0	1
Infection	3	0	8	1	0	0	4	1	4	0	0
Vomiting	0	1	1	10	0	0	0	0	4	5	0
Mucositis	1	2	5	3	1	0	4	0	3	2	0
Renal	9	1	1	0	0	1	8	1	0	0	0
Hepatic (ASAT/ALAT)	9	0	2	0	0	1	9	0	0	0	0
Pulmonary	12	0	0	0	0	0	9	0	0	0	0
Neurologic (paresthesias)	6	4	2	0	0	0	6	2	1	0	0

DISCUSSION

The present report describes a unique experience in the literature, with VAB-like chemotherapy regimens in ovarian germ cell cancer. The overall progression-free survival of 62% with a median follow-up of 7 years is satisfactory considering the results previously reported with other cisplatin-based regimens. However, an accurate analysis was required to distinguish dysgerminomas from non-dysgerminomatous tumours.

A review of the overall experience with the treatment of pure dysgerminoma shows that most patients can be treated by unilateral salpingo-oophorectomy alone, allowing preservation of reproductive capacity. However, treatment with surgery alone, even in stage I disease, results in an average recurrence rate of 20% [3–5, 18]. Therefore, additional therapy is necessary for patients with advanced disease as well as for some patients with stage I disease. Based on the radiosensitivity of dysgerminoma, several studies have reported excellent survival rates in the range of 60 to 100% with postoperative or salvage radiotherapy [3–5]. Chemotherapy was initially developed as an alternative procedure with the aim of avoiding the effects of radiotherapy on fertility [19]. In a report of the Gynaecologic Oncology Group experience, 19/20 patients with incompletely resected dysgerminoma, treated with either PVB or BEP (bleomycin + etoposide + cisplatin), were reported to be disease-free with a median follow-up of 26 months [6]. In another study from the M.D. Anderson Hospital (U.S.A.), 14 patients, of whom 11 had had all tumour resected, are disease-free after BEP regimen with a similar median follow-up [20]. In our series, the 2 patients who received VAB protocols as primary postoperative therapy and 1 of the 2 relapsing patients are alive without evidence of disease with a median follow-up of 5 years. All 3 patients recovered normal menstrual function, but none attempted pregnancy. These results are consistent with long-term curability and potential fertility preservation of cisplatin-based chemotherapy regimens. Whether low toxicity chemotherapy, such as carboplatin/etoposide combination, could replace standard regimens in pure dysgerminoma, especially in the adjuvant setting, warrants further investigation [21].

In patients with non-dysgerminomatous germ cell tumours, the impact of platinum-based chemotherapy regimens has dominated treatment approaches in recent years. After the promising results reported by Einhorn and Donohue in male germ cell cancer using the PVB regimen [11], several investigators documented high efficacy in the treatment of patients with non-dysgerminomatous tumours of the ovary. Despite the small numbers of cases and the short follow-up period, initial studies demonstrated a very high response rate [22–24]. However, subsequent reports with an adequate follow-up noted less favorable results [12, 13]. In the largest study performed by the Gynaecologic Oncology Group from 1978 to 1986, 89 patients with advanced or recurrent tumours were evaluated. 47 patients were free from progression at 2 years with a median follow-up of 52.5 months [12]. Therefore, a long-term progression-free survival of only 50–60% demonstrated the superiority of the PVB regimen over the VAC regimen [10] in patients with

advanced disease. Overall, these results were not impressive and required the investigation of alternative protocols.

With this background, we developed at the Institut Gustave Roussy an alternative approach with two VAB-like regimens. We based our programme on the results described by other investigators in male germ cell tumours [14–16]. Among 9 patients with no or minimal residual disease after initial surgery, two failures were seen. These results are reminiscent of the activity described with the PVB regimen in this setting [13, 22–24]. However, highly disappointing results were obtained in 8 patients with advanced or recurrent disease, since only two sustained complete remissions were observed, although two toxic deaths were registered, despite initial complete clinical response. These unacceptable toxicities were encountered with the AVAB regimen, which was therefore discontinued. The overall toxicity of the VAB-6 protocol was similar to that previously described in male patients [16] or with the PVB regimen in female patients [12, 13, 22–24].

In 1977, etoposide initially was shown to have single-agent activity in patients with refractory testicular cancer [25]. Subsequently, a multi-institutional, randomised trial reported the equal efficacy and less toxicity of the BEP protocol as compared with the PVB regimen in male germ cell cancer [26]. Early reports in patients with non-dysgerminomatous tumours of the ovary revealed excellent activity with etoposide-containing regimens [27, 28]. More extensive reports of experience with the BEP regimen confirmed these initial results [20, 29]. In a Gynaecologic Oncology Group trial, 50 of 52 patients with stages I–II and completely resected tumour were disease-free after three cycles of BEP [29]. Similar results with minimal toxicity were described by others [20]. However, the need for adjuvant chemotherapy in stage I disease has been questioned [30]. Investigators at the Charing Cross Hospital (London, U.K.) have suggested a close surveillance policy after initial careful staging. In a preliminary report, 11 patients were followed at monthly intervals during the first year and none have relapsed [30]. For patients with advanced disease, a response rate up to 80% was reported with the BEP regimen [20]. Similar high efficacy was described with an alternating chemotherapy schedule including intermediate dose methotrexate, cisplatin and etoposide (POMB/ACE regimen) [30]. These data favour etoposide- and cisplatin-based regimens as standard chemotherapy for germ cell tumours of the ovary.

The value of second-look surgery in the management of malignant ovarian germ cell tumours of the ovary is unclear. In our series, 10 patients underwent secondary surgery at completion of chemotherapy. In 4 patients with complete clinical response and normal serum tumour markers, histological findings were clearly negative. In 4 patients with normal serum tumour markers but residual masses, second-look laparotomy allowed excision of mature teratoma. Finally, 2 patients with abnormal markers at the time of surgery had active residual disease and eventually died. We suggest that second-look surgery is only mandatory for patients with normal tumour markers and residual masses at completion of chemotherapy.

According to the prognostic model developed in NSGCT of the testis at Institut Gustave-Roussy [17], we retrospectively assigned the patients to prognostic groups. In the good risk group, 1 of 10 patients died of progressive disease, and 1 patient experienced fatal renal toxicity, despite clinical complete response. In the poor prognosis group, only 1 is alive without evidence of disease and 1 patient died of liver toxicity in a complete response setting. These results suggest that a prognostic model based on serum tumour markers could be of interest in this population. No multivariate analysis has been published in malignant germ cell ovarian tumours, and further investigations are warranted to better define prognostic subgroups.

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Acknowledgement—The authors thank Catherine Molinazzi for her skilful secretarial assistance.

Pergamon

European Journal of Cancer Vol. 30A, No. 9, pp. 1244–1250, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00247-9

Medical Therapy of Malignant Nerve Pain. A Randomised Double-blind Explanatory Trial With Naproxen Versus Slow-release Morphine

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It is uncertain whether there exists a nociceptive component in malignant nerve pain responsive to NSAIDs and opioids. 20 patients with malignant nerve pain were randomly assigned to treatment with naproxen 1500 mg versus slow-release morphine 60 mg daily during 1 week, followed by cross-over medication during the second week in a double-blind, double-dummy protocol. In the 16 evaluable patients, a significant ($P < 0.05$) reduction of 26% (S.E. ± 7.9) in pain intensity was reached at day 7, compared to baseline pain. At day 7, significant pain relief of 32% ($P < 0.05$) was observed in the naproxen group, but not in the morphine group (21%, $P = 0.14$). Patients using morphine needed approximately twice as much paracetamol rescue than patients using naproxen. Additional pain relief could be observed in 4/9 patients with cross-over medication. These data support the concept of a nociceptive component in malignant nerve pain responding to NSAIDs and opioids, and favour the combination of both an anti-inflammatory drug and an opioid for symptomatic pain relief.

Key words: malignant nerve pain, nociceptive nerve pain, neuropathic pain, opioids, non-steroidal anti-inflammatory drugs naproxen, morphine
Eur J Cancer, Vol. 30A, No. 9, pp. 1244–1250, 1994

INTRODUCTION

NEUROPATHIC pain in cancer is usually severe, but unfortunately, response to treatment is often poor. Asbury and Fields have introduced the existence of two types of neuropathic pain: one nociceptive or inflammatory type of pain, which they designated as nerve trunk pain and one non-nociceptive type of pain designated as dysesthetic pain or deafferentation pain [1]. The concept of a nociceptive type of nerve pain is based on the assumption of an inflammatory reaction sensitising C-fibers travelling in the nerve trunk as induced by cancer or any other source of local ongoing tissue damage [2–5]. The dysesthetic type of nerve pain is associated with a previous nerve injury in the absence of ongoing tissue damage.

The clinical importance of distinguishing these two types of neuropathic pain is that their symptomatic treatment could be different. Deafferentation pain seems less responsive to anti-inflammatory drugs (NSAIDs) and opioids than nociceptive pain [6–10].

If the concept of nociceptive or inflammatory nerve pain holds true, one could expect that conventional analgesic drugs known to be effective for nociceptive pain, such as NSAIDs and opioids, may also produce relief of nociceptive nerve pain in cancer. Based on the positive results of a pilot study [11], we conducted a double-blind, double-dummy randomised explanatory trial in

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Revised 2 June 1994; accepted 24 June 1994.