Annals of Oncology 12: 967–974, 2001.

Original article

Randomized phase III trial of bleomycin, vindesine, mitomycin-C, and cisplatin (BEMP) *versus* cisplatin (P) in disseminated squamous-cell carcinoma of the uterine cervix: An EORTC Gynecological Cancer Cooperative Group study

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Summary

Purpose: Three previous mitomycin–cisplatin-based chemotherapy trials conducted within the EORTC Gynecological Cancer Cooperative Group (GCCG) in patients with disseminated squamous-cell carcinoma of the uterine cervix (SCCUC) suggested that with such regimens a higher overall response rate and a higher complete response rate could be obtained compared to what might have been expected from cisplatin alone. In that respect the combination of bleomycin, vindesine (Eldesine®), mitomycin C and cisplatin (BEMP) was the most promising. In the present study BEMP has been compared with the best single agent, cisplatin (P) in the expectation that improved response rates might translate into a better survival.

Patients and methods: Eligible patients were those with SCCUC and disseminated measurable disease outside previously irradiated areas, aged ⩽75 years, with a WHO performance status ⩽2 and adequate bone marrow, renal, hepatic and pulmonary function, who gave consent according to regulations followed in individual institutions. Patients were randomized to BEMP: E 3 mg/m^2 day 1, P 50 mg/m^2 day 1, B 15 mg (24-hour infusion) day 2–4 and M 8 mg/m^2 (at alternate cycles), or P 50 mg/m^2. The first four cycles were given every 3 weeks (induction phase). Subsequent cycles were given every four weeks (maintenance phase), during which B was deleted from BEMP (MEP). Patients failing on P could be treated with BEM. Of the 287 patients entered, 235 were eligible and 201 evaluable for response.

Results: BEMP induced a significantly higher response rate than P (42% vs. 25%, P = 0.006). There was no difference in complete response rate (11% vs. 7%). BEMP was significantly more toxic than P (± BEM), both with respect to hematologic and nonhematologic toxicities. After a median follow-up of 6.1 years, survival curves were not significantly different. Median progression-free survival and overall survival were 5.3 and 10.1 months with BEMP and 4.5 and 9.3 months with P (± BEM), respectively. In a multivariate analysis of prognostic factors for survival, a lower age (P = 0.003), a lower performance status (P = 0.0001) and a short (< 1 year) interval since diagnosis (P = 0.0152) were all associated with an increased risk of dying. For progression-free survival, lower age, prior radiotherapy, locoregional involvement and no prior surgery were associated with a high risk. Treatment with BEMP or P had no significant impact on survival, but for progression-free survival there was a trend in favor of BEMP (P = 0.0893). Adjusting for prognostic factors did not change the effect of treatment.

Conclusions: Combination chemotherapy with BEMP produces more toxicity and more responses compared with cisplatin alone in patients with disseminated SCCUC, but this does not translate into a better survival. Therefore, in the palliative setting single-agent cisplatin should remain the standard therapy for these patients.

Key words: cervix cancer, cisplatin combination chemotherapy, single-agent cisplatin

Introduction

Traditionally, chemotherapy has been limited to a palliative role in those patients with distant metastatic disease at presentation or recurrent disease following primary local therapy for whom salvage procedures – irradiation or pelvic exenteration – are inappropriate or have failed [1]. Several reviews on the role of chemotherapy in this setting have stressed the low single agent activity of conventional agents and indicated response rates in the range of 10% to 25% [2–6]. Cisplatin, even to-day, is considered the single most active cytotoxic agent [7, 8]. Contrary to what has been observed with the other conventional agents in the past, complete responses do occur, although in a low percentage (± 10%). Studies performed in the Gynecologic Oncology Group (GOG) in the US elucidated that there is no clear clinical relevant superiority of one dose or schedule of cisplatin [9, 10]. In a

large randomized trial, comparing cisplatin doses of 50 mg/m^2, 100 mg/m^2 (both on a single day) and 20 mg/m^2/day (for 5 consecutive days), all repeated every 21 days, overall response rates were 20.7%, 31.4% and 25.0%, and complete response rates were 10.0%, 12.7% and 8.6%, respectively [9]. There was no significant difference in response duration, progression-free interval or survival. The study concluded that a single dose of 100 mg/m^2 induced significantly more responses overall than a single dose of 50 mg/m^2, but this was not the case for complete responses. The additional conclusion was that, because of the increased toxicity with the higher dose and the lack of clinical benefit the use of the higher dose schedule was not justified. However, reaching a complete response appeared to be of benefit, as the survival in those patients was strikingly different from those in all other response categories. Whether that was a positive contribution of the drug itself or a selection due to the treatment of patients who anyhow would do better, was unclear.

Combination chemotherapy seems to increase the response rate up to 40% or 50%, although large variations in that (range 0%–93%) have been observed, mostly reflecting differences in sample size, methods of assessment of response and patient characteristics [1]. Again, as observed in the earlier mentioned large single agent cisplatin trial, patients who obtain a complete response seem to do better than those who do not. Three studies performed within the EORTC Gynecological Cancer Cooperative Group (GCCG) with several cisplatin–mitomycin C based regimens all suggested not only a higher overall response rate than usually seen with cisplatin alone, but also a higher complete response rate [11–13]. Some of the patients in complete response, in particular those with only lung metastases, showed a very long disease-free survival. This was in agreement with literature data suggesting that some of these patients even may be cured by chemotherapy [14, 15].

These observations posed a dilemma, i.e., should all patients be treated with cisplatin-based combination chemotherapy in order to increase the number of complete responses and, if not, is there a subgroup of patients that might benefit from this approach? A retrospective analysis of studies using cisplatin alone and those using cisplatin-containing combinations did not suggest that with the latter form of treatment much more complete responses could be obtained [1]. However, a definitive conclusion on that could only be made by performing a randomized phase III trial. We decided to do this by comparing cisplatin alone with BEMP, which consisted of a combination of bleomycin, vindesine, mitomycin C and cisplatin, and seemed to be the most efficacious regimen studied by the group at that time [12].

Patients and methods

Eligible patients included those women who had histologically confirmed advanced (stage IVB) or recurrent squamous-cell carcinoma of the uterine cervix (SCCUC) not suitable for curative treatment with surgery and/or radiotherapy. Patients had to have measurable lesions at distant sites outside previously irradiated areas and had to give informed consent. The latter had to be obtained according to the at that time operative regulations followed in the individual participating institutions.

Ineligible patients included those with malignancies of the cervix other than SCCUC, age > 75, a life expectancy < 3 months, a WHO performance status 3 or 4, prior chemotherapy, prior extensive radiotherapy within 8 weeks, previous or concurrent cancer at other sites, with the exception of adequately treated basal cell carcinoma of the skin, a serum creatinine level > 1.5 mg/dl (or > 132 µmol/l) and/or creatinine clearance < 60 ml/min/1.73 m^2, white blood cells (WBC) < 4000/mm^3 and/or platelet count < 100,000/mm^3, bilirubin > 1.5 mg/dl (or > 25.6 µmol/l), severe pulmonary dysfunction (MBC < 30 l/min, FEV_1 < 1000 cc), neurologic conditions which could interfere with evaluation of neurologic toxicity, or conditions of impaired mobility in which neurologic toxicity might cause an unacceptable degree of incapacity, bone lesions only detectable on bone scans, sclerotic bone metastases and serous effusions as single tumor response parameters, signs or symptoms of brain involvement or leptomeningeal disease, overt psychosis or senility.

Patients were prospectively stratified by participating institution, WHO performance status (0, 1 or 2), whether or not they had received radiotherapy to the pelvis, whether they had only distant metastases or loco-regionally recurrent disease also, and whether the distant metastases were only in lung and/or lymph nodes or also at other distant sites. Thereafter patients were randomized to receive BEMP or cisplatin alone (P). The BEMP schedule was given as follows. vindesine (Eldesine®) was given first at a dose of 3 mg/m^2 intravenously (i.v.) on day 1 (and repeated on day 8), followed by cisplatin 50 mg/m^2 given i.v. with appropriate hydration. Thereafter a continuous i.v. infusion of bleomycin (15 mg/day) was given for three days (day 2–4) followed at the end by an i.v. administration of mitomycin C 8 mg/m^2. The latter drug was to be given on alternate cycles (i.e., cycle 1, 3, 5 etc.). In the P arm cisplatin was given at the same dose as was given in the BEMP arm, i.e. 50 mg/m^2.

There were two phases in the treatment protocol; an induction phase (the first four cycles) and a maintenance phase. During the induction phase the regimens in both arms of the study were to be given every three weeks, during the maintenance phase every four weeks Patients were assessed for response after the first two cycles, after the first four cycles, and every three months thereafter or sooner if necessary.

If after the first two cycles there was progression of disease patients in the BEMP arm went off study (and treatment was at the discretion of the investigator), those in the P arm switched over to BEM (vindesine 3 mg/m^2, day 1 + 8; bleomycin 15 mg/day (day 1–3); mitomycin C 8 mg/m^2, day 4; every four weeks). All other patients, i.e., those responding or stable, continued for another two cycles of BEMP or P.

If after the first four cycles there was progression of disease patients in the BEMP arm went off study, and again treatment was left to the investigator. Patients in the P arm with progression at that time, but also those who were stable at that time, were supposed to receive BEM. Responders and stable disease patients in the BEMP then continued treatment, but without bleomycin (MEP: vindesine 3 mg/m^2, day 1 + 8; mitomycin C 8 mg/m^2, day 1 on alternate cycles; cisplatin 50 mg/m^2, day 1; every four weeks). Responding patients in the P arm continued with cisplatin at four-weekly intervals.

Dose adjustments were specified for hematologic, neurologic, hepatic, renal and pulmonary toxicity or dysfunction from other causes. Toxicity was graded according to WHO criteria [16]. With respect dose modification for myelosuppression, all modifications were carried out referring to counts measured on day 1 (with the exception of the vindesine dose on day 8 in the MEP regimen, where it is adjusted according to the counts on the same day). If WBC are < 2000/mm^3 and/or platelets < 50,000/mm^3 on day 1 the schedule was postponed for one week (maximum two weeks during the induction phase). If the delay was more than two weeks during the induction phase the patient went off study.

All patients were planned to receive at least two cycles of chemotherapy unless there was rapidly progressive disease, such that further treatment was not in the best interest of the patient. Patients in whom a complete response was obtained either by BEMP or P continued treatment for another six cycles from the moment complete response was recorded. Thereafter treatment was stopped. Patients with partial response continued treatment in both arms of the study until disease progression became evident of excessive toxicity occurred. The same was true for patients with stable disease in the BEMP arm. As mentioned earlier, those with stable disease in the P arm after four cycles were supposed to receive BEM as second-line treatment.

Complete response was defined as complete disappearance of all clinically detectable tumor(s) together with a return of relevant blood chemistries to normal values for at least four weeks. Partial response was defined as a 50% or more decrease in total tumor size of the lesions(s) which was measured or evaluated to determine the effect of therapy by two observations not less than four weeks apart. This was to be found in the absence of progression of any lesion or appearance of a new lesion(s). Stable disease (or no change) was defined as a change of less than 50% reduction or less than 25% increase in the size of one or more measurable of evaluable lesions for the duration of at least 12 weeks.

Statistical considerations

The main endpoint of the study was the response rate. The target difference to observe was an increase from 25% (with cisplatin alone) to 45% with BEMP. Based on the accrual in previous studies it was expected that 140 patients (70 in each arm) could be accrued in less than three years, allowing a 80% power for observing the difference if it existed (with $\alpha = 0.05$). Patients were to be followed until death to allow for a comparison of survival. If the combination resulted in an increase of at least 50% in the median survival the power for detecting it would be near 80% ($\alpha = 0.05$). For the comparison of toxicities the Wilcoxon test and the chi squared test for trend were used. Survival curves were constructed according to Kaplan–Meier and compared with log-rank analysis or a test for linear trend, where appropriate. A prognostic factor analysis was performed including the following prognostic factors: treatment, age, performance status, prior radiotherapy, extent of disease (i.e., only distant metastases or locoregional involvement also), site of the metastases (only lung/lymph nodes or also elsewhere), interval since diagnosis, FIGO stage, prior surgery, initial blood counts (WBC and platelets). For this, first a univariate analysis was performed to asses the individual prognostic value of all variables; second, these variables were included in a Cox model with the treatment indicator; third a Cox model was fit including all variables and treatment; fourth, a backward selection procedure was performed on a Cox model including all prognostic variables and treatment. These analyses were performed for both survival and progression-free survival.

Results

From September 1986 to December 1991 251 patients were enrolled. Based on an interim analysis, thereafter the study was kept open only for patients with only lung and/or lymph node metastases in order to allow for a further analysis of that specific subgroup. However, only 36 patients were accrued in the additional years and the study was closed in May 1996. Although 40 institutions participated in this study, 70% of the enrolled patients were derived from 12 institutions. Of the 287 enrolled patients, 235 fulfilled the criteria of eligibility and 197 were fully evaluable (i.e., evaluable for both response and toxicity), while an additional 26 were only partially evaluable (4 for response). Reasons for not being eligible were; disease stage, extent or pathology ($n = 25$), measurability ($n = 12$), performance status ($n = 7$), prior therapy ($n = 3$), no data ($n = 5$). The characteristics of all randomized patients are summarized in Table 1. The median number of treatment cycles in the BEMP arm was significantly lower than in the P (± BEM) arm: four (range 0–16) *versus* six (range 0–17) ($P = 0.0017$). Of note, only 45 patients in the P arm received BEM as second-line treatment. Due to the increased toxicity experienced in the BEMP arm (see below), dose reductions and dose delays occurred more frequently in the BEMP than in the P arm. As result of this, the dose intensity of cisplatin was different in the two arms, i.e., median 13.9 mg/m^2/week (range 9.3–20.8 mg/m^2/week) with BEMP and 15.2 mg/m^2/week (range 4.3–17.8 mg/m^2/week) with P ($P = 0.0002$). Graphically this is depicted in Figure 1.

Table 1. Patient and disease characteristics.

	BEMP ($n = 143$)	P ($n = 144$)
Number of eligible patients	119	116
Age (years)		
Median	53	52
Range	25–72	28–76
WHO performance status		
Median	1	1
Range	0–2	0–3
Prior treatment		
Prior radiotherapy (unknown)	101 (3)	110 (4)
Prior surgery (unknown)	60 (4)	68 (2)
Prior chemotherapy (unknown)	3 (3)	0 (4)
Prior hormones (unknown)	1 (5)	0 (4)
Initial disease stage (FIGO)		
I–IV	113	112
IVB (IVB without RT)	17 (16)	13 (9)
Unknown	13	19
Extent of disease		
Distant metastases (DM) only	69	68
DM plus locoregional disease	69	71
Unknown	5	5
Site of metastases		
Only lung and/or lymph node mets	93	93
Elsewhere	41	43
Unknown	9	8
Histologic cell type		
Squamous	129	136
Other	14	8
Squamous cell type		
Keratinizing	42	49
Large-cell non-keratinizing	39	40
Small-cell non-keratinizing	20	18
Unknown	28	29

Toxicity

There was more frequent and more severe hematologic and nonhematologic toxicity observed in the BEMP arm than in the P arm (Tables 2 and 3). This was not only the case in the first two cycles, when all evaluable patients indeed received BEMP or P, but also when all treatment

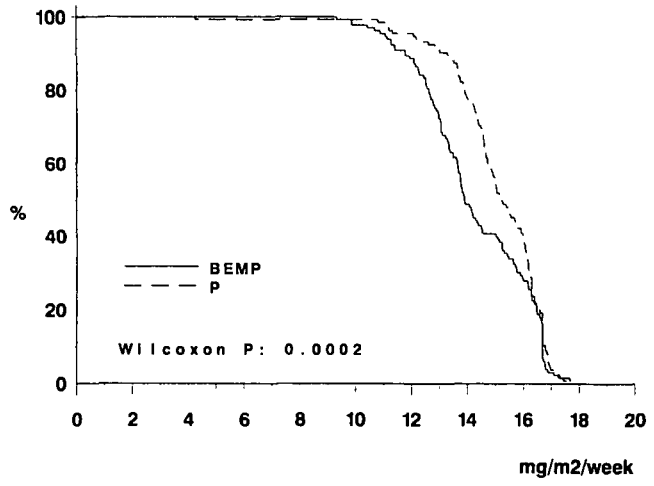

Figure 1. Dose intensity (mg/m^2/week) during treatment with combination chemotherapy (BEMP) and during single-agent cisplatin (P).

Table 2 BEMP *versus* P – hematologic toxicity.[a]

Time of assessment	Number of evaluable patients WBC/platelets	Median nadir value (× 1000/mm^3)	
		WBC	Platelets
First two cycles			
BEMP	48/46	2.2	197
P	40/39	4.7	245
P-value[b]	0.0001	0.0218	
All cycles			
BEMP	62/60	1.9	160
P → BEM	47/46	3.8	208
P-value	0.0001	0.0063	

[a] Worst nadir analysis
[b] Wilcoxon test.

cycles were taken into account, i.e., also patients who received BEM after P. Table 2, summarizing the hematologic toxicity, shows a worst nadir analysis, in which counts on days 1, 8, 15, and 22 were taken into account. With respect to nonhematologic toxicity, several toxicities did occur in a similar frequency in the two arms of the study. These include: local toxicity at the site of the infusion, nausea and vomiting, diarrhea, oral toxicity, pulmonary toxicity, infection, cardiac toxicity, neuropathy, consciousness, or changes in blood pressure. However, this can be explained by the fact some patients experienced additional toxicities when they received BEM after P. Indeed, in the first two cycles infection, diarrhea, stomatitis and neuropathy occurred significantly more frequent with BEMP than with P (Table 3). Skin toxicity occurred also more frequently in the BEMP arm (P = 0.061). There were five early deaths in the BEMP arm and two in the P arm. Two of these in each arm were due to malignant disease. The others (all with BEMP) included a sepsis with acute renal dysfunction, a case of bleeding from the tumor, without thrombocytopenia or evident tumor progression and one patient died of unknown cause at home. Because of the reported dyspnea,

Table 3 BEMP *versus* P – nonhematologic toxicity.[a]

Type of toxicity	First two cycles			All cycles		
	BEMP	P	*P*-value[b]	BEMP	P	*P*-value[b]
Alopecia	80 (33)	12 (1)	0.001	88 (57)	45 (22)	0.001
Drug fever	35 (1)	5 (0)	0.001	40 (1)	21 (2)	0.008
Diarrhea	29 (2)	12 (1)	0.006	37 (2)	21 (2)	0.145
Infection	16 (3)	2 (0)	0.001	19 (5)	13 (2)	0.120
Stomatitis	13 (2)	3 (0)	0.004	17 (2)	14 (1)	0.329
Neuropathy	11 (1)	3 (0)	0.009	33 (5)	24 (2)	0.062
Allergy	2 (0)	0 (0)	0.175	9 (2)	0 (0)	0.002

[a] In percentages, any grade (grade 3 and 4).
[b] χ^2-test for trend.

Table 4 Response rates and their 95% confidence intervals.

	BEMP rate (95% CI)	P rate (95% CI)	*P*-value
All entered patients	n = 143	n = 144	
Response rate	35 (27–43)	20 (14–27)	0.005
Complete response	9 (5–15)	6 (2–11)	0.250
All eligible patients	n = 119	n = 116	
Response rate	42 (33–51)	25 (17–33)	0.006
Complete response	11 (5–16)	7 (3–13)	0.279
All evaluable patients	n = 93	n = 108	
Response rate	54 (43–64)	27 (18–35)	0.001
Complete response	14 (8–23)	7 (3–14)	0.129

toxicity of bleomycin or mitomycin C could have played a role, but was uncertain. If only grade 3 and 4 toxicities were taken together and the incidence was compared between the two arms, then significant differences were noticed in the first two cycles for both hematologic toxicity (20 of 143 vs. 0 of 144, P = 0.001) and nonhematologic toxicity (19 of 143 vs. 6 of 144, P = 0.006). When all cycles were taken into account then only the incidence of grade 3 and 4 hematologic toxicitiy remained significantly more frequent with BEMP (33 of 143 vs. 6 of 144, P = 0.001), while grade 3 and 4 nonhematologic toxicity occurred in a similar fashion. In these analyses nausea, vomiting and alopecia were excluded.

Response and survival

BEMP induced significantly more responses than P. However, no difference in complete response rate was found. This observation was done irrespective of eligibility status or evaluability status (Table 4). However, the fact that no significant difference in complete response rate was observed might simply have been a result of insufficient numbers, because in fact complete response rates doubled when only evaluable patients were taken into account. Both for BEMP and for P it was evident that complete response rates depended on the category of patients explored. It was highest in the most favorable

Table 5 Median survival and progression survival with 95% confidence intervals (in months).

	BEMP (95% CI)	P (95% CI)
Survival		
All entered patients	10.1 (8.3–12.5)	9.3 (8.1–11.2)
Only distant metastases	11.5 (8.7–13.7)	10.1 (8.0–11.7)
Only lung a/o lymph node mets	12.9 (10.1–16.8)	11.3 (9.5–16.5)
FIGO stage IVB	9.7 (5.0–13.2)	10 3 (8.1–16.2)
Progression-free survival		
All entered patients	5.3 (4.0–7.0)	4.5 (4.0–5 0)
Only distant metastases	6.9 (4.7–7.0)	5.1 (3.6–6.2)
Only lung a/o lymph node mets	7.4 (4.7–9.5)	5.9 (4.0–7.1)
FIGO stage IVB	4 2 (1.9–7.6)	4.1 (3.2–6.2)

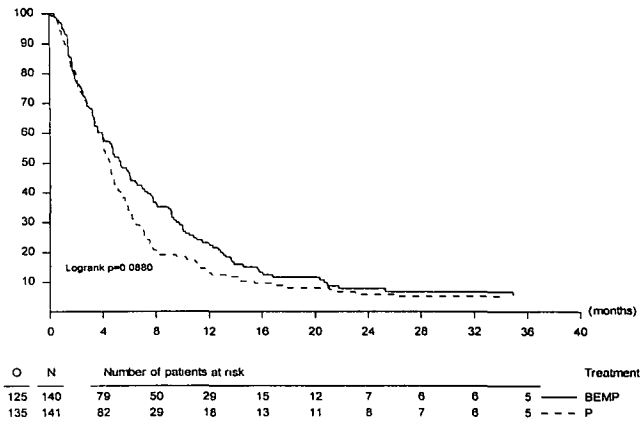

Figure 2. Progression-free survival of all patients in the BEMP arm and the P arm for whom survival data are available.

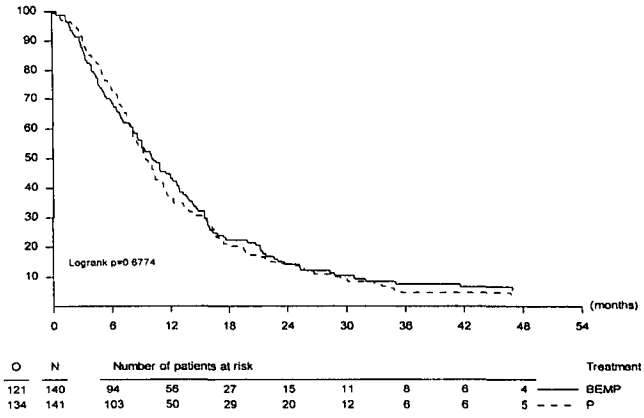

Figure 3 Overall survival of all patients in the BEMP arm and the P arm for whom survival data are available.

patient group, i.e. those with only lung and/or lymph node metastases and no locoregional disease. In this latter category 11 of 42 (26%) patients achieved a complete response on BEMP *versus* 5 of 40 (13%) patients on P (P = 0.118). Among the patients who responded, this was first documented in the first cycle for 39 (78%) patients receiving BEMP and for 14 (49%) of the receiving P. In the second cycle, another five (10%) responded to BEMP and 11 (40%) to P. So, responses occurred early in both arms. The median duration of response among those who did respond was 9.2 months and 7.1 months for BEMP and P, respectively. For patients with only lung and/or lymph node metastases and no locoregional disease the median duration of response was 11.5 months and 7.2 months for BEMP and P, respectively, and for those with stage IVB disease it was 7.6 and 7.5 months, respectively.

Median progression-free survival and overall survival figures with their 95% confidence intervals (CI) are given in Table 5. There was neither a significant difference in progression-free survival nor in overall survival between the two arms of the study (Figures 2 and 3), although for the first a trend in favor of BEMP existed.

In a prognostic factor analysis on all eligible patients 11 variables were included: treatment, age, performance status, prior radiotherapy, prior surgery, extent of disease (i.e., only distant metastases or distant metastases with locoregional involvement), the localisation of the metastases (i.e., only lung and/or lymph node metastases or also elsewhere), FIGO stage, initial WBC and initial platelet count. The risk ratios of treatment did not change when a correction was done for potential prognostic factors. In a backward selection procedure on the Cox model including all prognostic factors and treatment the following variables were retained in the model when the analysis was done for survival: age (P = 0.0003), performance status (P = 0.0001), and interval since diagnosis (P = 0.0152). Lower age, lower performance status and an interval since diagnosis of less than one year were all associated with an increased risk of dying. In the analysis for progression-free survival, next to age (P = 0.0031), prior radiotherapy (P = 0.0176), prior surgery (P = 0.0099) and extent of disease (P = 0.0214) were retained in the model. Lower age, prior radiotherapy, no prior surgery and locoregional involvement were associated with a high risk.

Discussion

Our study showed that aggressive platinum-based combination chemotherapy produced significantly more toxicity and a higher response rate compared with cisplatin alone in patients with disseminated SCCUC, but this did not translate into survival benefit. In that sense our study is in agreement with those of others, who reported on direct comparisons between cisplatin alone and combinations including cisplatin [17, 18]. In those two other studies cisplatin dose was the same as in our study, i.e. 50 mg/m^2, both in the single-agent reference arm and in the combination arms.

The Southwest Oncology Group reported on a randomized phase II trial of a four-drug regimen VBMP (vincristine, bleomycin, mitomycin-C, cisplatin), a two-drug regimen MP, and cisplatin as a single agent. Although that study was not designed as a phase III comparison, the results suggested no significant differences in objective response rates to the three different treatment [17]. The overall objective response rates for

cisplatin, MP, and VBMP treated patients were 33%, 25%, and 22%, respectively. Also response duration or survival duration seemed not between the three regimens. Median survival durations associated with cisplatin, MP, and VBMP treatment were 17.0, 7.0, and 6.9 months, respectively. However, the comparison was hampered by the fact that the third arm, cisplatin only, was dropped early because of poor accrual (doctors bias), and the study continued only into the two combination arms. Severe or life threatening leukopenia and thrombocytopenia were observed in 18%–24% of patients treated with VBMP and MP, but in none of those receiving cisplatin alone.

The large Gynecologic Oncology Group phase III study of cisplatin *versus* cisplatin plus mitolactol (dibromodulcitol) *versus* cisplatin plus ifosfamide was performed in 454 patients, and again showed no improvement in survival with these combinations [18]. Nevertheless, one of these combination regimens (cisplatin plus ifosfamide) had a significantly higher response rate (31.1% vs. 17.8%, $P = 0.004$) and progression-free survival (4.6 vs. 3.2 months, median; $P = 0.003$) compared to cisplatin alone. This gain was obtained at the cost of greater toxicity. Leukopenia, renal toxicity, peripheral neurotoxicity and central nervous system toxicity were significantly more frequent with cisplatin plus ifosfamide ($P < 0.05$).

From that GOG study some promise was expected from the addition of bleomycin to the cisplatin plus ifosfamide combination, because of promising data from this so-called BIP regimen in some phase II studies [19, 20]. In those studies overall response rates varied from 66.6% to 69% and complete response rates were 19% and 20%. In a comparative (but not randomized) study of BIP *versus* cisplatin alone in a limited number of patients ($n = 106$), performed by the same group of investigators who reported on the promising phase II data, BIP did not seem to improve survival, while it induced two toxic deaths in the 56 patients who received it [21]. Other investigators reported much less favorable results with BIP and stressed the considerable toxicity which it can induce [22]. Clearly the emphasis in future studies should be placed on the development of more active single agents and combinations or various novel treatment approaches.

There are several new cytotoxic agents which seem to be of interest for future studies, either alone or in combination with existing active conventional agents. These agents are the taxoids paclitaxel and docetaxel [23–25], the topoisomerase I inhibitors irinotecan and topotecan [26–31], the vinca-alkaloid vinorelbine [32–34] and the antimetabolite gemcitabine [35, 36]. Combinations of these newer agents with cisplatin in phase II studies have resulted in response rates varying from 41% to 67%, each with 95% confidence intervals, which are overlapping with those obtained in earlier platinum-based regimens not including these newer agents [37–41]. It is therefore questionable whether these newer combinations will have any impact on the survival of patients with recurrent or metastatic cervical cancer. Randomized comparisons of such newer combination *versus* cisplatin alone seem warranted. However, this is only defensible when adequate numbers of patients are included in such studies and preferably quality of life studies are integrated. In the set up of such studies it is of importance to take into account important factors which may have impact on the chance to response to chemotherapy. Whatever type of chemotherapy is used, results are influenced by characteristics such as age and performance status of the patient, the site of the disease involved (pelvic or extrapelvic), the extent of the disease (distant metastases only or together with locoregional disease), the location of the metastases, and whether the lesions are located in a previously irradiated area [1, 42]. From the multivariate analysis performed in the GOG phase III trial, comparing cisplatin plus mitolactol *versus* cisplatin plus ifosfamide *versus* cisplatin alone a significant association was found between survival duration and initial performance status (PS of 0 was more favorable, $P < 0.001$) and age (younger was unfavorable, $P = 0.025$). The outcome of the multivariate analysis in our study was completely in agreement with this: both a lower age ($P = 0.003$) and a lower performance status ($P = 0.0001$) were associated with an increased risk of dying. In addition, a shorter interval since initial diagnosis seemed to have a negative influence ($P = 0.0152$). Lower age, prior therapy with radiotherapy or no prior surgery and locoregional involvement all had a negative impact on progression-free survival in our study.

Outside trials, the use of cisplatin alone is still the gold standard if one decides to use chemotherapy for palliation. The use of more aggressive regimens, which all result in considerable toxicity remains questionable. An individual approach to these patients is warranted, whereby identification of a subset of patients who indeed might benefit from chemotherapy is a major issue. Any decision for treatment of cervical cancer patient in the palliative setting should be assessed against the benefit of best supportive care, which may provide the best option for some of these patients.

*Appendix

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Received 24 January 2000; accepted 1 February 2001.

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