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Epirubicin Plus Medroxyprogesterone as Second-Line Treatment of Advanced Prostatic Cancer

A Study by the Italian Trials in Medical Oncology Group

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The evaluation of drug efficacy in patients with advanced prostatic cancer who have progressed to hormonal therapy is difficult, although palliation of the pain related to bone involvement still represents an important endpoint. In this study, epirubicin (EpiADM) plus medroxyprogesterone acetate (MPA) were given to advanced prostatic cancer patients with symptomatic bone involvement who had progressed to hormonal therapy. EpiADM was administered at a dose of 30 mg/m^2 i.v. weekly and MPA at a daily dose of 1,000 mg p.o. for the first month and 500 mg thereafter. Fifty-four patients entered the trial, all of whom were evaluable. Amelioration of pain and a ≥50% reduction in analgesic intake were observed in 52% of cases, with a mean duration of 4 months. Of the 28 responsive patients, 26 had already received two lines of hormonal therapy or were resistant to first-line therapy. Of the 23 patients with measurable lesions, 6 obtained a ≥50% tumor shrinkage at these sites. The treatment was well tolerated, and no cardiac toxicity was observed up to a total cumulative EpiADM dose of 660 mg/m^2. In conclusion, this regimen seems to have a palliative effect in patients with advanced prostatic cancer who have progressed to hormonal therapy, and it is feasible in an outpatient setting.

Key Words: Advanced prostatic cancer—Second-line therapy—Response criteria.

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In Europe, the estimated incidence of prostatic cancer is of 85,000 newly diagnosed cases a year, which represents 13% of all male cancers (1). Approximately 50% of prostatic cancer patients have bone involvement at the time of diagnosis (2). In these cases, the suppression of androgenic activity is considered the most adequate first-line medical treatment. Unfortunately, hormonal therapy is successful in only 60–80% of cases, and the median duration of response is no more than 12–18 months (3). Relapsing patients, and those refractory to hormonal therapy, have a poor quality of life as a consequence of bone pain and limited survival (4), and clinicians generally agree on the need to identify an effective and safe second-line medical treatment.

Over the past decade, a weekly doxorubicin schedule has been proposed as an effective and feasible second-line treatment for advanced prostatic cancer (5). Subsequent studies with epirubicin (EpiADM) confirmed preliminary observations, and suggested that these compounds were active in relieving pain and achieved a certain tumor regression and a reduction in tumor markers (6,7). The weekly schedule appeared to be less cardiotoxic than 3-weekly administrations, and was well tolerated even in an elderly population such as that represented by prostatic cancer patients (8).

Other studies have suggested that intermediate-high doses of medroxyprogesterone acetate (500–1,000 mg/day) are effective in palliating bone pain in advanced prostatic cancer, with episodic tumor regressions (9–12). Furthermore, many reports have indicated that medroxyprogesterone decreases testosterone serum

levels through the inhibition of luteinizing hormone secretion (10,13,14).

On the basis of these results, and laboratory data suggesting a good level of synergy between epirubicin and medroxyprogesterone (15), it was decided to carry out a multicenter study within the Italian Trials in Medical Oncology (ITMO) group. The main aim of the study was to define the efficacy of this combination in ameliorating bone pain and reducing analgesic intake in prostatic cancer patients with symptomatic bone involvement, who had progressed to at least first-line hormonal therapy.

PATIENTS AND METHODS

Eligible Patients

The eligibility criteria included histologically diagnosed prostatic cancer, the presence of symptomatic bone involvement, an age ≤ 78 years, an ECOG performance status (PS) 1–3, progression to at least a first-line hormonal therapy, no previous chemotherapy, the absence of previous or concomitant cardiovascular diseases (such as uncontrolled hypertension, dysrhythmias, myocardial infarction, or congestive heart failure), serum creatinine ≤ 1.2 mg% and bilirubin ≤ 1.5 mg/dl, white blood cell count ≥ 4,000 mm^3, platelets ≥ 100.000 mm^3, hemoglobin ≥ 8 g/dl. Patients concomitantly receiving steroids, biphosphonates, vitamin D, or calcitonin were excluded from the study, as were patients who needed concomitant radiotherapy or who had ended radiotherapy within the 4 weeks preceding study entry.

Staging Procedures and Treatment Scheme

Pretreatment examinations included a detailed medical history with special attention being paid to the assessment of the severity of bone pain and the recording of the type and doses of the analgesics taken. Pain severity was classified according to the McGill-Melzack intensity scale: 0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating (16). Hemogram and blood chemistry, prostatic specific antigen (PSA), chest radiograph, abdomen-pelvis computed tomography scans or ultrasound, and bone radiograph and scan were also performed. Cardiac function was assessed by means of blood pressure measurements, electrocardiogram, and the determination of LVEF through myocardial scan. Except for the hemogram and blood pressure measurements (which were repeated weekly), these examinations were performed every 2 months and at the moment of treatment withdrawal. Weekly assessments were made of the evolution of bone pain and changes in analgesic medicaments.

Eligible patients were treated with epirubicin 30 mg/m^2 weekly in a bolus intravenous injection and daily oral doses of medroxyprogesterone 1,000 mg for the first 30 days and 500 mg thereafter. The treatment was administered in an outpatient setting.

Criteria for Response Evaluation

Response was defined as an improvement (recognized by both the patient and the physician) of at least one grade in bone pain, and a concomitant reduction in the dose of all analgesics of at least 50%. In patients not receiving analgesics, response was evaluated only on the basis of changes in bone pain. Pain relief and the reduction in analgesic intake had to be maintained for at least 1 month before the patient was considered responsive. Time to response was calculated from the beginning of treatment to the detection of response. Response duration was calculated from the time of its onset to the time in which one or both of the response parameters (bone pain or analgesic intake) worsened. Measurable lesions and bone disease were also assessed and evaluated according to WHO criteria (17). A decrease in prostatic specific antigen was defined as a reduction of at least 50% in baseline values, confirmed at two successive determinations.

Treatment Continuation

In responding patients (i.e., an amelioration of bone pain and a reduction in analgesic intake), epirubicin plus medroxyprogesterone were continued until progression (i.e., the worsening of pain and/or an increase in analgesic intake), or until the total cumulative dose of epirubicin reached 990 mg/m^2. In the case of no variation in pain and/or analgesic intake, treatment was stopped after an epirubicin cumulative dose of 480 mg/m^2.

Toxicity Monitoring

Side effects were reported according to WHO criteria (17). In particular, in the presence of myelotoxicity, epirubicin treatment was delayed by 1–2 weeks until recovery (white blood cell count ≥ 4,000 mm^3, platelets ≥ 100,000 mm^3, hemoglobin ≥ 8 g/dl). In the case of clinically or instrumentally detected cardiac toxicity, treatment was stopped.

Statistical Analysis

Survival was estimated by means of the Kaplan-Meier method and calculated for all eligible patients.

Exact 90% confidence limits based on binomial distribution were computed for the probability of response.

Between-strata comparisons of response probability were performed by means of the Fisher exact test for contingency tables.

RESULTS

Patient Characteristics

Between December 1989 and October 1992, 60 patients were registered at the ITMO central office in Milan; 6 patients were considered ineligible because of the lack of symptomatic bone involvement. Of the 54 eligible patients, all were evaluated for response and toxicity. The characteristics of the patients are reported in Table 1. All of the cases had received at least one first-line hormonal therapy, and 29 were resistant to initial hormonal manipulations. Ten of the 54 cases did not routinely require analgesics; the rest were receiving nonsteroidal anti-inflammatory drugs or morphine derivates.

TABLE 1. *Patient characteristics*

Evaluable	54
Age	
Median	65
Range	48–78
Performance score (ECOG)	
1/2	10/34
3	10
Level of pain	
Mild/discomforting	10/34
Distressing	10
Previous hormonal therapy	
LH-RH analogues + antiandrogens	38
LH-RH analogues or castration	10
Antiandrogens	6
Presence of measurable lesions[a]	23/54
Pelvic nodes	9
Lung ± pelvic nodes	6
Liver ± pelvic nodes	5
Subcutis	2
Supraclavicular nodes	1
Baseline PSA values	
Normal/elevated (≥2N)	17/37

ECOG, Eastern Cooperative Oncology Group; LH-RH, luteinizing hormone-releasing hormone; PSA, prostatic specific antigen.
[a] Excluding prostate.

Response to Treatment

Table 2 shows subjective responses to treatment both in patients regularly taking analgesics and in those not routinely treated with analgesic drugs. In the latter, response was evaluated by observing variation in pain, recognized by both the patient and the physician, persisting for at least 1 month. Table 3 shows those patients who stopped taking analgesics because of the complete disappearance of bone pain. As can be seen, 9 of the 44 patients (20%) receiving analgesics at study entry discontinued their use for a median time of 5 months. The patients who experienced an amelioration in bone pain and concomitantly reduced their analgesic intake by at least 50% are reported in Table 4. Of the 28 responding patients, 20 had already received luteinizing hormone-releasing hormone analogues or orchiectomy plus antiandrogen, and 6 of the remaining 8 were resistant to a first-line hormonal therapy consisting of orchiectomy or antiandrogens.

In order to assess the direct antitumor activity of the epirubicin-medroxyprogesterone combination, measurable lesions, bone disease and prostatic specific antigen were investigated both before and after treatment (the results are reported in Table 5). Bone disease was considered with the sole aim of evaluating tumor progression, because the ubiquitous presence of blastic metastases did not allow any sign suggesting recalcification to be identified. Of the patients with baseline measurable lesions, 26% (90% confidence interval: 15–42%) showed a tumor shrinkage of at least 50%. Of the 28 subjective responders, 3 patients experienced a tumor shrinkage ≥ 50% (lung in one case, pelvic nodes in the remaining two). In the group of 26 nonresponders, the total disappearance of tumor lesions was reported in two cases (liver in one patient and pelvic nodes in the other), and a tumor shrinkage ≥ 50% in one case (pelvic nodes). A decrease in prostatic specific antigen was observed in 3 of the 37 cases with high baseline values, all 3 experiencing a concomitant subjective response.

Median survival for the 54 evaluable patients was 12 months (Fig. 1).

Cardiac Toxicity

Of the 54 evaluable patients, three (5%) experienced cardiac toxicity, which manifested itself in the form of congestive heart failure. In two cases, the damage was

TABLE 2. *Subjective responses*

Severity of pain	No. improved patients/ total patients	% (confidence interval)	Time to response[a] weeks (range)	Duration[a] months (range)
Not requiring analgesics	5/10	50 (20–80)	4 (3–6)	3 (1+, 7)
Requiring analgesics	23/44	52 (41–64)	4 (2–8)	4 (1+, 12)

[a] Mean values.

TABLE 3. *Patients who stopped analgesics due to pain relief*

Age years	Type of analgesic	Baseline doses mg/day	Time to response weeks	Duration months
67	Buprenorfine	0.4	3	8
	Diclofenac (Voltaren)	100		
66	Buprenorfine	0.8	2	4
	Diclofenac	200		
78	Nimesulide	400	2	2+
73	Diclofenac	200	2	5
73	Diclofenac	200	3	7
68	Diclofenac	300	3	3
67	Naproxene	550	3	5+
78	Diclofenac	100	3	5+
65	Diclofenac	200	3	7+

detected instrumentally as a consequence of a decrease in LVEF of, respectively, 15% and 26%; in the third patient, congestive heart failure was diagnosed clinically and confirmed instrumentally as a decrease in LVEF of 25%. All three patients were undergoing treatment at the time of the discovery; treatment withdrawal led to the complete recovery of all of them. In none of these cases was congestive heart failure observed below a total cumulative epirubicin dose of 660 mg/m^2, and two of them had reached a total cumulative dose $\geq$ 900 mg/m^2. The patient who developed congestive heart failure after 660 mg/m^2 of epirubicin was 72 years old, had not reported any history of heart disease, and his congestive heart failure was diagnosed instrumentally as a decrease in LVEF of 15%.

No other cardiac toxicity was detected.

Other Side Effects

After a mean of 12 epirubicin cycles (range: 5–33), the following WHO grade 1/2 side effects were observed: leukopenia (17/6 patients), nausea/vomiting (17/3 patients), alopecia (4/5 patients), hydric retention (6/2 patients), anemia (1/4 patients), thrombocytopenia (5/– patients), mucositis (4/– patients), hyperglicemia (1/– patient). No grade 3-4 side effects were observed, except in three patients who experienced grade 3 leukopenia; however, two of these patients had previously been treated with radiotherapy to the pelvis. In no case did toxicity determine a patient's refusal to continue treatment.

DISCUSSION

The evaluation of drug efficacy in advanced prostatic cancer is extremely difficult and uncertain. This is mainly due to the fact that most patients have blastic bone involvement, whereas only 20–30% show visceral or soft tissue lesions (2). Furthermore, in these latter patients, the evolution of measurable sites is not always correlated to subjective improvement (18). The same is true for prostatic specific antigen determinations. It has been observed that the assessment of prostatic specific antigen values in patients treated with second-line therapy may not reflect real tumor evolution (19). It therefore appears to be fundamental to identify specific and objective criteria for the assessment of baseline symptoms and their evolution. To this end, the use of a specific questionnaire has been proposed (20). In an attempt to evaluate pain improvement by objective means, the patients in our study were considered responsive only if the amelioration in bone pain was associated with a reduction of at least 50% in the doses of all analgesics. This was possible in 44 patients, since 10 cases were not routinely taking any analgesic, and were therefore evaluated only considering pain modifications.

In the 54 evaluable patients treated with the epirubicin plus medroxyprogesterone combination, we observed a 52% subjective response rate; the mean time to response was 4 weeks, and the mean response duration 4 months. Tumor shrinkage > 50% was obtained in 26% of patients with measurable lesions. The role of epirubicin in the amelioration of performance status and in the induction of objective responses still requires definition. Further investigations are needed in order to assess whether a more feasible and less expensive single-agent treatment with medroxyprogesterone could obtain the same results as those observed in this study with the combination. In our opinion, epirubicin played a relevant role in inducing the 26% objective tumor shrinkage observed in this trial; previous experiences with medroxyprogesterone, although demon-

TABLE 4. *Patients who reduced analgesic doses by at least fifty percent*

Type of analgesic (no. of pts)	Baseline doses[a] mg/day (range)	Doses after treatment[a] mg/day (range)	Time to response[a] weeks (range)	Duration[a] months (range)
Diclofenac (6)	90 (50–200)	35 (10–100)	4 (3–8)	6 (2–12)
Ketorolac (6)	35 (20–40)	17 (10–20)	5 (3–7)	3 (1–4)
Buprenorfine (2)	0.8	0.2	4 (2–6)	2 (1–3+)

[a] Mean values.

TABLE 5. *Objective antitumor activity and correlation between subjective and objective responses*

	Total: 54 pts	Subjective response: 28 pts (%)	Not subjective response: 26 pts (%)
Baseline measurable lesions	23	8	15
Tumor shrinkage ≥ 50%	6	3 (37)	3 (20)
Tumor progression or no change	17	5 (63)	12 (80)
Bone progression[a]	18	8 (29)	10 (38)
High baseline prostatic specific antigen	37	20	17
Lowered	3	3 (15)	—
Unchanged or worsened	34	17 (85)	17 (100)

[a] Clearly documented by radiologic means.

strating palliation of pain, have reported objective tumor regressions only in sporadic cases (9–12).

As far as side effects were concerned, the treatment was well tolerated and feasible. Three cases of cardiotoxicity were reported, but none of them occurred before the total cumulative dose of epirubicin had reached 660 mg/m^2, and two of them only after a total cumulative dose ≥ 900 mg/m^2. It must be emphasized that only 1 of 54 patients showed a symptomatic congestive heart failure. In all cases, the damage was reversible on treatment withdrawal. It is therefore suggested that patients should be monitored by means of myocardial scan after a total cumulative dose of 480 mg/m^2 is reached, and thereafter at every increase of 120 mg/m^2 up to 840 mg/m^2, when the treatment could be stopped. On the basis of the presented data, this should practically eliminate cardiac toxicity. Other noncardiologic side effects were mild, leukopenia being the only grade III side effect reported (in 3 of 54 patients). Even grade II side effects were unusual, being observed in less than 12% of cases. Anemia (grade 1–2) and thrombocytopenia (grade 1) were observed in 5 patients, respectively, but in these cases it remains difficult to assess whether this was determined by treatment toxicity or by bone marrow infiltration.

Other authors have already reported on the combination epirubicin plus medroxyprogesterone in 30 patients who had progressed to hormonal therapy, although the drugs were given sequentially rather than concomitantly. Their results were equivalent, with 25/30 patients showing subjective improvement and episodic regressions of tumors and markers. The achievement of subjective improvement did not lead to any improvement in survival for this set of patients (21).

In two randomized studies, a comparison was made between epirubicin plus medroxyprogesterone and estramustine in the treatment of patients who had progressed to hormonal therapy (22,23). It was observed that the combination appeared to be superior to estramustine in inducing subjective improvement and prolonging time to progression. Furthermore, one of these two randomized studies suggests that the combination of epirubicin and medroxyprogesterone was more effective than single epirubicin administration (22).

In conclusion, this paper suggests that the combination of epirubicin and medroxyprogesterone may be active and feasible in the palliation of advanced prostatic cancer pretreated with hormonotherapy. For the future, it is to be hoped that the duration of subjective response will be improved, and that an assessment can be made as to whether a single-agent treatment with

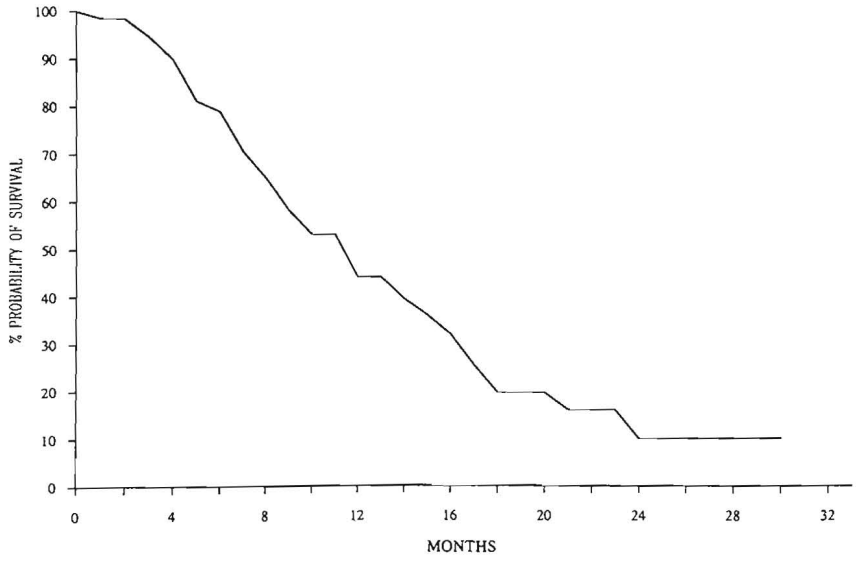

FIG. 1. Overall survival.

medroxyprogesterone at high doses, certainly less expensive and better tolerated than the combination, may be similarly effective. The study also outlines the need to determine more adequate response criteria, based on subjective and objective parameters, to be adopted for the evaluation of drug efficacy in the second-line treatment of advanced prostatic cancer.

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