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ANTI-TUMOUR TREATMENT

The role of doxorubicin and epirubicin in the treatment of patients with metastatic hormone-refractory prostate cancer

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Summary Advanced hormone-refractory prostate cancer (HRPC) is characterized by prevalently osteoblastic bone metastases which are what mostly affect these patients' quality of life and make the assessment of response to treatment particularly difficult by commonly used criteria. HRPC cannot be cured by any available therapeutic option, and chemotherapy has to be still considered as a palliative treatment. The anthracyclines doxorubicin (Dox) and epirubicin (Epi), alone or in combination with other agents, have been extensively used in the treatment of HRPC, but controversial results have been reported. The majority of reviewed studies reported a pain reduction in >50% of patients receiving Dox or Epi, suggesting a substantial palliative effect by their use in metastatic HRPC. The weekly schedule of anthracyclines seemed to achieve similar results to the 3-weekly schedule but with a better toxicity profile. Although the toxic adverse effects were usually manageable when anthracyclines were combined with other agents, toxicity was severe by a number of aggressive regimens. Docetaxel is today approved for the treatment of HRPC, and must be considered the standard platform on which new agents may be combined. Given that HRPC includes a heterogeneous group of patients with variable rates of tumour growth, the combination of docetaxel with active agents such as anthracyclines may deserve further clinical investigation.

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Introduction

Historically, the treatment of patients with hormone-refractory prostate cancer (HRPC) has led to disappointing results, with most of the chemotherapy trials showing low response rates and a minimal impact on survival.^{1,2} Nevertheless the activity of antitumoural agents on HRPC is difficult to determine because up to 90% of the patients have bone metastases, and the standardized response criteria commonly used in other solid tumours are inadequate.³ For this reason, surrogate end-points have been developed, such as changes in serum PSA levels and bone markers.^{4,5}

A $\geq 50\%$ decline in PSA serum levels and time to PSA progression are considered appropriate outcome measures in more recent phase II trials, but they do not always indicate direct benefit to patients and a clear improvement in overall survival.⁶ Pain is a common and disabling complication of the disease, and its assessment is a validated method for the evaluation of symptom control in clinical studies and can be considered a real endpoint.^{7,8}

The results of two large randomised trials have recently provided substantial support in favour of the role of chemotherapy in the treatment of HRPC by demonstrating that docetaxel and prednisone and docetaxel and estramustine enhance survival in comparison with older regimens, and significantly improve the quality of life.^{8,9} Although docetaxel chemotherapy has become the first-line standard of care for HRPC, PSA responses rarely exceed 50% and median survival is less than 20 months, thus the use of chemotherapy in this disease remains a subject of active clinical investigation. Combination treatments with docetaxel and other agents such as calcitriol, thalidomide, and bevacizumab, chemotherapies such as satraplatin and ixabepilone, as well as a variety of immunotherapeutic approaches, are promising, but results of phase III trials are needed to confirm the activity and safety of these drug combinations.^{10–13}

Out of all the chemotherapeutic agents, anthracyclines rank among the most important anticancer drugs with a large spectrum of antitumoural activity, including prostate cancer. These compounds can intercalate with DNA, directly affecting transcription and replication, and are able to form a tripartite complex with topoisomerase II and DNA, affecting DNA repair and leading to apoptosis.¹⁴ Anthracyclines may induce apoptosis also in the cells of prostate carcinoma that overexpress the *bcl-2* oncogene.¹⁵ Of note, the prognosis of HRPC has been associated with a *bcl-2* oncogene overexpression which protects the tumour population from the apoptotic phenomenon induced by most chemotherapeutic agents.¹⁶ Anthracyclines also generate free radicals in both normal and malignant tissues, and exert direct effects on the cell membranes, upsetting calcium and sodium regulation and intracellular electron transport.¹⁷

Doxorubicin (Dox), or adriamycin, and its analogue epirubicin (Epi), or 4-epidoxorubicin, are well-known anthracyclines which are usually administered in a large variety of tumours.¹⁸ Epi is a stereoisomer of Dox and this change has little effect on the mechanism of action and spectrum of activity of Epi compared with Dox, but it introduces several consequences on its physical and chemical properties, with pharmacokinetic and metabolic changes such as in-

creased volume of distribution, 4-*O*-glucuronidation, and consequent enhanced total body clearance or shorter terminal half-life. Dox recommended dose usually ranges from 60 to 75 mg/m² every 3 weeks, or 20 mg/m² as a single weekly dose. Epi is given as a single agent in usual doses of 90 to 120 mg/m² every 3 weeks or 30 mg/m² as a single weekly dose.^{18,19}

The major acute toxicity of Dox and Epi is bone marrow suppression. Cardiomyopathy, which manifests itself clinically as congestive heart failure (CHF), may occur if cumulative drug doses of Dox exceed 500 mg/m², while Epi was soon used at cumulative doses almost double those of Dox (900 mg/m² vs. 500 mg/m² respectively), resulting in equal activity but not in increased cardiotoxicity.²⁰ Dox and Epi, alone or in combination with other agents, have been extensively used in the treatment of HRPC, but controversial results have been reported. The aim of this review is to discuss the efficacy and toxicity of the anthracyclines Dox and Epi as first-line treatment for patients with HRPC.

Methods

The Medline databases were searched up to January 2008 using disease-specific terms (prostate cancer, hormone-refractory prostate cancer, metastatic prostate cancer), and treatment-specific terms (chemotherapy prostate cancer, doxorubicin prostate cancer, epirubicin prostate cancer, anthracyclines prostate cancer). Articles published as formal papers in peer-reviewed journals were selected for inclusion if they reported outcomes of interest including tumour response, time to disease progression, survival, quality of life, and adverse events of treatment. A total of 38 phase II studies and 13 randomized phase II–III studies were reviewed.

Dox/Epi alone

A number of clinical studies has assessed the activity and tolerability of Dox or Epi alone as first-line treatment for patients with HRPC (Tables 1 and 2). Toxicity has been evaluated according to World Health Organization (WHO) criteria or, more recently, according to the National Cancer Institute common toxicity criteria version 2.0.

The first clinical experiences with Dox/Epi alone were performed in the 1980s, in the pre-PSA era, and reported objective response (OR) on measurable lesions ranging from 5% to 55%.^{21–30} Three-weekly Dox was associated with a haematologic toxicity profile comparable to 3-weekly Epi, while toxicity of 3-weekly anthracyclines was generally worse than weekly schedule: Epi 75–100 mg/m² every 3 weeks exhibited about 35–40% grade 3–4 haematologic toxicity and about 19% grade 3–4 nausea and vomiting.

Of note, the majority of these studies reported an improvement in bone pain in symptomatic HRPC patients. A point to consider is that before the PSA-era classic response rates could be exclusively determined in the minority of patients with measurable disease, and controversy existed as to whether these patients were representative of advanced prostate cancer patients in general who only had metastases to bone. Moreover, different response criteria were often used, and results on pain reduction were

Table 1 Efficacy of Dox/Epi alone in patients with metastatic HRPC

Treatment schedule	N	% PSA response	% OR	Pain reduction	OS	Reference
Dox 60 mg/m ² /3w	12	NA	25.0	NA	6.5	21
Dox 20 mg/m ² /w	25	NA	33.0	67.0	10.2	24
Dox 25–60 mg/m ² /3–4w	52	NA	5.0	NA	NA	22
Dox 20 mg/m ² /w	22	NA	9.5	28.5	8.5	23
Epi 25 mg/m ² /w	60	NA	36.0	87.0	12.0	25
Epi 25 mg/m ² /w	21	NA	NA	69.0	15.0	27
Epi 90 mg/m ² /4w	29	NA	55.0	48.0	9.0	26
Dox 20 mg/m ² /w	54	NA	NA	69.0	9.7	28
Dox 25 mg/m ² /w	24	14.8	9.5	33.3	8.0	32
Epi 30 mg/m ² /w	48	20.0	11.1	37.7	12.5	
Epi 75 mg/m ² /3w	26	NA	12.0	NA	5.0	29
Epi 100 mg/m ² /3w	39	32.0	24.0	NA	NA	30
Epi 35 mg/m ² /w	32	81.0	28.0	29.0	NA	40
Epi 30 mg/m ² /w	148	24.0	0	56.0	13.0	38
Epi 25 mg/m ² /w	38	22.0	4.0	66.1	10.5	41
Epi 100 mg/m ² /4w	41	27.0	8.0	69.0	10.7	

CTX = cyclophosphamide; MMC = mitomycin C; 5FU = 5-fluorouracil; MTX = methotrexate; P = prednisone; K = ketoconazole; MPA = medroxyprogesterone acetate; CDDP = cisplatin; DES = Diethylstilbestrol; EMP = estramustine; VBL = vinblastine; S = suramin; E = etoposide; Dex = dexametasone; CBDDP = carboplatin; Pac = paclitaxel; V = vinorelbine; D = docetaxel.

N = enrolled patients.

NA = not assessable.

OR = objective response on measurable lesions.

w = weekly.

OS = overall survival (median, months).

Lip = liposomal.

Neutr = neutropenia.

Thr = thrombocytopenia.

Table 2 Grade ≥ 3 toxicity (%) of Dox/Epi alone in patients with metastatic HRPC

Treatment schedule	N	Neutr	Anemia	Thr	Nausea vomiting	Cardiac	Stomatitis mucositis	Reference
Dox 60 mg/m ² /3w	12	NA	NA	NA	16.7	0	0	21
Dox 20 mg/m ² /w	25	0	NA	1	0	0	0	24
Dox 25–60 mg/m ² /3–4w	52	NA	0	NA	15.0	16.6	0	22
Dox 20 mg/m ² /w	22	0	0	4.7	0	0	0	23
Epi 25 mg/m ² /w	60	0	0	0	0	0	0	25
Epi 25 mg/m ² /w	21	0	0	0	0	NA	0	27
Epi 90 mg/m ² /4w	29	0	0	0	0	0	0	26
Dox 20 mg/m ² /w	54	NA	NA	NA	NA	NA	NA	28
Dox 25 mg/m ² /w	24	NA	NA	NA	9.5	19.0	0	32
Epi 30 mg/m ² /w	48	NA	NA	NA	0	0	0	
Epi 75 mg/m ² /3w	26	34.6	NA	0	19.2	NA	NA	29
Epi 100 mg/m ² /3w	39	41.0	16.0	3.0	18.0	5.3	5.3	30
Epi 35 mg/m ² /w	32	12.5	12.5	3.2	0	0	0	40
Epi 30 mg/m ² /w	148	8.0	7.0	3.0	0	0	0	38
Epi 25 mg/m ² /w	38	5.0	5.0	0	18.0	3.0	0	41
Epi 100 mg/m ² /4w	41	0	10.0	0	29.0	0	2.0	

See Table 1 for abbreviations.

rarely accompanied by precise data regarding analgesic use and overall quality of life. However, despite these limitations in the analysis of older studies, published data suggest a substantial palliative effect by the use of anthracyclines in metastatic HRPC. This finding appears particularly interesting because, as it is the duration and quality of survival that is important to patients, palliation can be considered a real endpoint.

In the PSA-era, after previous encouraging results, a randomized phase II study evaluated the activity and tolerability of weekly Dox 25 mg/m² and weekly Epi 30 mg/m² in 72 HRPC patients: PSA response was 14.8% in the Dox arm and 20.0% in the Epi arm, with a reduction in bone pain in 33.3% and 37.7% of patients, respectively.^{31,32} Haematologic toxicity, nausea, vomiting, and oral mucositis were generally mild, either with weekly Dox than with weekly Epi; CHF oc-

curred in four patients (19%) receiving weekly Dox between the 9th and 13th course of chemotherapy, while Epi exhibited less cardiotoxicity than Dox. Although CHF was rarely observed with weekly anthracyclines alone, the potential risk of cardiotoxicity must be considered with the use of this class of agents. In this setting, it has been documented that the probability of incurring Dox-induced CHF is related to the total dose of Dox administered, with a continuum of increasing risk as the cumulative amount of administered drug increased, and weekly Dox is associated with a significantly lower incidence of CHF over the conventional 3-weekly schedule.^{33,34} Moreover, the assessment of cardiotoxicity by endomyocardial biopsy demonstrated that weekly Dox is associated with less anthracycline-induced damage than the 3-weekly schedule.³⁵ Although Dox or Epi administration led to identical morphologic pattern of cardiac damage, it has been reported that Epi caused less endomyocardial injury than Dox.^{36,37}

An extended study confirmed the safety and the palliative effect of weekly Epi in HRPC: 73 (56%) of 131 evaluable patients had a reduction in bone pain and an improvement in performance status, and the median global quality of life improved in 68% of the patients after 12 treatment cycles.³⁸ The same researchers evaluated the activity of anthracyclines also by a neoadjuvant study in which patients received weekly Epi and hormonal therapy before surgery: 35–75% reduction in tumour size and a >50% PSA decrease were observed in all patients, and they were able to undergo successful prostatectomy.³⁹

Another study with weekly Epi reported that 81% of HRPC patients had a >50 decline in PSA levels, and about 29% had a reduction in bone pain.⁴⁰

A small randomized trial was performed in order to determine the impact of the different administration regimens of Epi on health related quality of life in 79 patients with HRPC: one group received Epi 25 mg/m² every week and the other received Epi 100 mg/m² every 4 weeks.⁴¹ No improvement in quality of life was observed, and there were no significant differences between groups in response rates and survival. Despite a reduction in bone pain was observed in more than 65% of patients in both treatment arms, the authors concluded for disappointing results with the use of anthracyclines alone in metastatic prostate cancer. However, several patients with unfavourable prognostic factors such as poor performance status, very old age and low haemoglobin level were included. In this study, as well as other previous experiences, the effect on pain symptomatology was not associated with favourable results as measured by standardized criteria for measurable lesions or biochemical response.^{23,28,32,38,41} These findings confirm the difficulty to accurately monitor patients with metastatic HRPC, who are mostly affected by painful bone metastases. In the absence of large controlled randomized comparisons, the majority of trials with Dox or Epi alone suggested a median survival (5–13 months) similar to that usually observed in untreated patients (6–12 months).

Dox/Epi combined with other chemotherapy agents

Several clinical studies have assessed the activity and toxicity of Dox or Epi in combination chemotherapy regimens as first-line treatment for patients with HRPC (Tables 3 and 4).

In the beginning of 1980s, a few studies investigated the association of Dox and cyclophosphamide (CTX) and reported OR ranging from 0% to 51.7%; a randomized study found no statistically significant difference in terms of OR, progression-free survival and overall survival between Dox + CTX compared with MTX alone or cisplatin (CDDP) + 5-fluorouracil (5FU) + CTX.^{42–46} The tolerability of Dox combined with CTX was reported to be acceptable, while fixed-dose Dox plus dose-escalated CTX was associated with grade 4 neutropenia and febrile neutropenia in 8% of all cycles, and the combination of Dox, MTX and CTX achieved 20% grade 3–4 neutropenia.

A very small randomized trial compared 3-weekly Dox and CDDP over Dox alone: time to progression and survival were similar in the two treatment arms, while myelotoxicity and gastrointestinal toxicity were severe with the combination regimen.⁴⁷

The association of Dox, mitomycin C (MMC) and 5-FU was also investigated, but severe toxicities, particularly myelosuppression, were usually encountered.^{48–52}

An interesting antitumour activity was reported with the combination of Dox and ketoconazole (K): 58% OR, 55% PSA response, and 15.5 months of median survival were observed in 38 assessable patients with measurable soft tissue disease.⁵³ In this study, 46% of patients had not undergone prior antiandrogen withdrawal. Nevertheless, the majority of older studies have not controlled for this endocrine withdrawal syndrome: about 20–25% of patients with progressive HRPC treated with combined androgen blockade have a significant decrease in serum PSA level when antiandrogen is discontinued, and some of the patients experience a clear symptomatic or objective improvement.⁵⁴ The association of Dox and K exhibited 29% grade 3–4 neutropenia, unusual toxic reactions on the skin associated with grade 3–4 stomatitis (29%) and mucositis (13%), and two patients had a sudden cardiac death. The alternating schedule KAVE including Dox, estramustine phosphate (EMP), vinblastine (VBL) and K was subsequently investigated, and achieved promising results in terms of PSA decrease, OR, pain reduction and extended survival.^{55,56} However, severe neutropenia, thromboembolic events, and cardiotoxicity, with 6% early death, were observed.

A phase II study reported substantial palliative effect and acceptable toxicity with weekly Epi combined with medroxyprogesterone acetate (MPA), while a randomized trial described that heart failure was frequently observed in patients receiving this combination regimen.^{57,58} No significant difference in overall survival was found between patients who received weekly Dox 20 plus prednisone (P) or P alone.²⁸

Since a significant synergistic antitumour effect had been demonstrated in vitro in testosterone-sensitive human prostate carcinoma cell line LNCaP with the combination of Epi and the polysulfonated naphthylurea suramin (S), some investigators tested this combination in HRPC patients.⁵⁹ Despite the in vitro promising data, the results obtained with Epi combined with S did not seem to represent a major improvement in the treatment of this disease, compared with anthracyclines alone.^{60,61} In addition, severe neurotoxicity and nephrotoxicity were described.

Other treatment options including anthracyclines were subsequently investigated, and further suggested the

Table 3 Efficacy of Dox/Epi combined with other chemotherapy agents in patients with metastatic HRPC

Treatment schedule	N	% PSA response	% OR	Pain reduction	OS	Reference
Dox 30 mg/m ² /d 1–8/4w + CTX	22	NA	32.0	NA	11.0	42
Dox 50 mg/m ² /4–9w + MMC + 5-FU	62	NA	51.7	NA	NA	48
Dox 20–40 mg/m ² /3w + CTX	68	NA	32.0	26.0	6.7	44
Dox 40 mg/m ² /4w + MMC + 5-FU	15	NA	NA	71.0	8.3	49
Dox 30 mg/m ² /4w + MMC + 5-FU	15	NA	NA	64.0	NA	50
Dox 60 mg/m ² /3w + CDDP	17	NA	14.0	40.0	10.1	47
Dox 50 mg/m ² /3w + CTX	60	NA	0	NA	10.6	45
Dox 30 mg/m ² /4–5w + MMC + 5-FU	70	NA	7.1	NA	8.6	51
Dox 40–50 mg/m ² /3w + CTX + MTX	50	NA	18.7	NA	8.0	43
Epi 20 mg/m ² /w + P	59	NA	NA	30.3	9.5	28
Dox 35–50 mg/m ² /4–8w + MMC + 5FU	68	NA	NA	NA	10.0	52
Dox 20 mg/m ² /w + K	39	55.0	58.0	NA	15.5	53
Epi 30 mg/m ² /w + MPA	54	NA	26.0	52.0	12.0	57
Dox 40 mg/m ² /3w + CTX	35	46.0	33.0	NA	11.0	46
Epi 60 mg/m ² /3w + CDDP + EMP	28	NA	NA	89.4	15.0	65
Epi 40 mg/m ² /3w + CDDP + 5-FU	21	38.0	14.2	NA	8.0	67
Epi 100 mg/m ² /3w + EMP	24	54.0	0	29.1	NA	62
Epi 25 mg/m ² /w + S	10	0	0	NA	NA	60
Dox 20 mg/m ² /2w + K + EMP + VBL	46	67.0	75.0	76.0	19.0	55
Dox 20 mg/m ² /w + EMP	31	58.0	45.0	27.0	12.0	63
Epi 25 mg/m ² /w + S	26	33.0	27.0	65.0	8.0	61
Epi 100 mg/m ² /3w + CDDP	22	32.0	14.0	38.0	NA	66
Dox 50 mg/m ² /3w + EMP	29	NA	57.1	NA	10.7	64
Dox 20 mg/m ² /w + K + VBL + EMP	34	56.0	47.0	NA	23.4	56
Epi 30 mg/m ² /2w + E + Dex	32	50.0	40.0	48.0	10.5	68
Dox 50 mg/m ² /3w + DES	74	NA	27.0	NA	9.1	69
Epi 50 mg/m ² /4w+CBDDP + 5-FU/FA	80	57.0	45.0	65.0	9.2	70
Epi 30 mg/m ² /w + Pac	32	57.0	48.0	56.0	12.9	72
Dox 20 mg/m ² /w + V + P	46	42.0	NA	NA	14.2	71
Epi 30 mg/m ² /w + D	39	68.4	37.5	72.7	21.5	73

See Table 1 for abbreviations.

palliative effect of these agents when included in combination regimens for the treatment of metastatic HRPC. Anthracyclines combined with EMP achieved interesting palliative results, but severe hematologic, gastrointestinal, and cardiac toxicity were reported.^{62–65} A substantial hematologic and cardiac toxicity was observed also with the combination of Epi and CDDP, while a better tolerability was found with low-dose Epi, CDDP and protracted 5FU infusion.^{66,67}

Interesting results in terms of response rate and improvement in pain symptomatology, with a favourable toxicity profile, were recently reported with Epi combined with oral etoposide (E) and low-dose dexamethasone (Dex).⁶⁸ Severe cardiotoxicity was reported with the combination of Dox and diethylstilbestrol (DES), which was 10 times more frequent over Dox alone.⁶⁹ The aggressive regimen of Epi, carboplatin (CBDDP) and 5-FU achieved favourable results but reported a number of dose reductions and treatment delays which make this treatment not suitable for the majority of patients.⁷⁰

A statistically significant improvement in quality of life, with a reduction in bone pain compared with baseline was described with the combination of weekly Dox 20 mg/m² i.v. and vinorelbine (V) 20 mg/m² i.v. plus P 5 mg twice daily.⁷¹ However, 36.9% grade 3–4 neutropenia was observed,

three patients experienced pulmonary emboli which were fatal in two cases, and two patients died of acute myocardial infarction.

A few studies investigated the combination of anthracyclines with taxanes: a good activity and a favourable toxicity profile were reported with weekly Epi combined with weekly paclitaxel (Pac).⁷² The combination of weekly Epi 30 mg/m² and weekly docetaxel (D) 30 mg/m² achieved a >50% PSA decrease in 68.4% of 38 evaluable patients, and rapid pain reduction in 72.7%, with an overall median survival of 21.5 months.⁷³ This combination regimen was well tolerated and severe cardiotoxicity was not observed, probably thanks to the administration of a weekly schedule and the adoption of a stop-and-go strategy. Although Epi combined with D proved to be an active and safe regimen also in a few phase I/II studies on breast cancer, the median cumulative dose of Epi reached in these reports (less than 500 mg/m²) was too low to draw firm conclusions about the cardiac safety of combining Epi with D, and further investigation is needed.^{74,75} It seems that Epi combined with D, and anthracyclines combined with dose-escalating CTX, or with EMP, K and VBL (KAVE regimen), or with CBDDP and 5FU/FA, achieved the best results in terms of biochemical response and palliation in HRPC (Table 3). However, it is difficult to make comparisons between trials due to the heterogeneity

Table 4 Grade ≥ 3 toxicity (%) of Dox/Epi combined with other chemotherapy agents in patients with metastatic HRPc

Treatment schedule	N	Neutr	Anemia	Thr	Nausea vomiting	Cardiac	Stomatitis mucositis	Reference
Dox 30 mg/m ² /d 1–8/4w + CTX	22	13.6	NA	9.0	NA	NA	4.5	42
Dox 50 mg/m ² /4–9w + MMC + 5FU	62	NA	9.6	NA	NA	1.6	NA	48
Dox 20–40 mg/m ² /3w + CTX	68	4.4	NA	4.4	NA	NA	NA	44
Dox 40 mg/m ² /4w + MMC + 5FU	15	21.4	42.8	28.5	0	NA	0	49
Dox 30 mg/m ² /4w + MMC + 5FU	15	7.0	0	13.0	0	0	NA	50
Dox 60 mg/m ² /3w + CDDP	17	18	NA	12	6	NA	NA	47
Dox 50 mg/m ² /3w + CTX	60	NA	NA	NA	24	7	7	45
Dox 30 mg/m ² /4–5w + MMC + 5FU	70	64.0	NA	21.0	NA	NA	NA	51
Dox 40–50 mg/m ² /3w + CTX + MTX	50	20.0	NA	0	NA	NA	2.0	43
Epi 20 mg/m ² /w + P	59	NA	NA	NA	NA	NA	NA	28
Dox 35–50 mg/m ² /4–8w + MMC + 5FU	68	60.2	4.4	17.6	11.7	NA	5.9	52
Dox 20 mg/m ² /w + K	39	29.0	NA	0	5.0	2.5	42.1	53
Epi 30 mg/m ² /w + MPA	54	5.0	0	0	0	5.0	0	57
Dox 40 mg/m ² /3w + CTX	35	NA	NA	NA	0	0	0	46
Epi 60 mg/m ² /3w + CDDP + EMP	28	NA	NA	NA	NA	3.5	0	65
Epi 40 mg/m ² /3w + CDDP + 5FU	24	14.0	14.0	5.0	14.0	0	0	67
Epi 100 mg/m ² /3w + EMP	24	33.3	0	8.3	4.1	12.5	0	62
Epi 25 mg/m ² /w + S	10	0	0	10.0	0	0	10.0	60
Dox 20 mg/m ² /2w + K + EMP + VBL	46	6.6	NA	0	4.4	4.4	4.4	55
Dox 20 mg/m ² /w + EMP	31	38.7	0	0	6.4	0	0	63
Epi 25 mg/m ² /w + S	26	4.0	0	0	0	0	0	61
Epi 100 mg/m ² /3w + CDDP	22	80.9	28.5	42.8	9.5	14.2	4.7	66
Dox 50 mg/m ² /3w + EMP	29	15.3	23.0	3.8	15.3	3.8	0	64
Dox 20 mg/m ² /w + K + VBL + EMP	34	29.4	8.8	2.9	8.8	8.8	5.8	56
Epi 30 mg/m ² /2w + E + Dex	32	12.0	0	0	0	0	0	68
Dox 50 mg/m ² /3w + DES	74	NA	NA	NA	9.5	13.6	0	69
Epi 50 mg/m ² /4w + CBDDP + 5FU/FA	80	33.8	16.0	16.0	10.6	1.3	5.3	70
Epi 30 mg/m ² /w + Pac	32	6.0	6.0	0	0	0	0	72
Dox 20 mg/m ² /w + V + P	46	36.9	NA	2.3	0	4.3	0	71
Epi 30 mg/m ² /w + D	38	15.8	13.1	7.8	2.6	0	0	73

See Table 1 for abbreviations.

of the evaluated populations and treatment strategies, and the small sample size of most analyzed studies. In addition, the initial reports included several patients with poor performance status, while most of recent trials enrolled patients at the first evidence of hormone refractoriness, and only patients with ECOG performance status of ≤ 2 . The combination of weekly Epi and D achieved an extended survival, which was obtained also by weekly Dox combined with EMP, VBL and K, by the alternating KAVE regimen.^{55,56,73} On the basis of recent studies on metronomic chemotherapy, it may be intriguing to believe that the apparently favourable prognosis of these groups of patients might be due also to the antiangiogenic effects of low i.v. doses of anthracyclines given at frequent intervals.^{76,77} The continuous or metronomic low-dose chemotherapy is a method for administering cytostatics at a low and well-tolerated concentration without prolonged breaks. As antiangiogenic effects cause antitumour effects, low-dose chemotherapy given continuously could enhance the antiangiogenic effect resulting in a marked antitumour effect.⁷⁸

Liposomal anthracyclines

A few small studies evaluated the activity of liposomal Dox, a polyethylene glycol-coated liposomal formulation of Dox, in patients with HRPc, but reported disappointing results in

terms of PSA response and pain reduction.^{79–81} A randomized study evaluated liposomal Dox at two different dosages in 48 patients: a significant decrease in pain levels in 28.6% and 52.6% of cases in the two treatment arms, respectively, was observed.⁸² Liposomal encapsulation of Dox 40–50 mg/m² every 4 weeks was associated with less severe haematologic toxicity than that observed with Dox given in weekly and 3-weekly schedule.⁸⁰ However, grade 3–4 gastrointestinal side effects and grade 3 skin toxicity with palmar-plantar erythrodysesthesia (PPT) were reported with this formulation of Dox, and a more common incidence of PPT (45%) was also observed with the use of reduced dose of liposomal Dox (25 mg/m²) administered every 2 weeks.^{81,82} The available studies seem to suggest that the liposomal formulation of Dox is not superior to Dox or Epi alone in the treatment of HRPc.

Mitoxantrone

Mitoxantrone (M) is an anthracenedione which has a chemical structure similar to Dox but a significantly lower toxicity profile. After the first promising results, two large trials compared M + P versus P alone, or M + hydrocortisone (H) versus H alone.^{7,83} A >50% PSA decrease and pain relief were obtained by 31% and 29% of patients receiving M/P and by 22% and 12% of patients receiving P alone ($p = 0.01$); a

>50% PSA decrease was found in 38% of patients in the M/H group and in 22% of patients in the H group. Hematologic toxicity was the main adverse event with M. Despite these randomized trials reported no benefit of M in terms of overall survival, the combination of M with corticosteroids became a standard treatment for HRPC. Afterwards, the randomized trial TAX327 compared M and P with D and P.⁸ Treatment with 3-weekly D led to superior survival, improved biochemical response and pain reduction, as compared with M/P. The randomized trial SWOG-9916 compared M plus P with D plus EMP: there was a significant improvement in overall survival for the D/EMP group, while no significant difference in pain reduction was observed between the two treatment arms.⁹ Severe gastrointestinal, metabolic and neurologic toxicity was reported with D/EMP treatment.

Recently, in the attempt to deliver full doses of chemotherapy avoiding overlapping toxicity and preserving dose intensity, the sequential administration of M/P and D/EMP was investigated. However, this treatment strategy did not appear to improve D activity in HRPC patients, while several adverse events such as deep venous thrombosis, liver toxicity, and CHF were observed.^{84,85} A multicenter phase II study evaluated the combination of D 60 mg/m² every 3 weeks and M 8 mg/m² every 3 weeks in asymptomatic HRPC patients. Treatment-related adverse events included neutropenia (16%), anemia (3%), and two deaths due to myocardial infarction. Although a long median survival (25.7 months) was reported, the low response data (25.6% PSA decrease) and the observed toxicity in this selected group of asymptomatic patients do not seem to suggest M as ideal partner of D in HRPC.⁸⁶

Conclusions

Advanced HRPC is characterized by prevalently osteoblastic bone metastases which are what mostly affect these patients' quality of life and make the assessment of response to treatment particularly difficult by commonly used criteria. HRPC cannot be cured by any available therapeutic option, and chemotherapy has to be still considered as a palliative treatment. This review analyzed all relevant clinical studies concerning the use of anthracyclines Dox and Epi in the treatment of HRPC, and suggested that both drugs are effective in this disease as a single agent and in combination chemotherapy regimens. The substantial improvement in bone pain demonstrated by most of studies makes Dox and Epi useful drugs for the treatment of symptomatic HRPC patients. Docetaxel is today approved for the treatment of HRPC, and there are ongoing clinical trials to investigate the activity and safety of docetaxel combined with novel agents. In this scenario, given that HRPC includes a heterogeneous group of patients with variable rates of tumour growth, the combination of docetaxel with active chemotherapeutic drugs such as anthracyclines may deserve further clinical investigation. Specifically, the combination of docetaxel and anthracyclines might have a role in symptomatic HRPC patients who present unfavourable prognostic factors which reflect the biologic aggressiveness of the tumour. Moreover, Dox and Epi have a favourable cost-effectiveness

ratio. The weekly schedule of anthracyclines seems to achieve similar results to the 3-weekly schedule but with a better toxicity profile, and therefore it is preferable in patients with metastatic HRPC who are mostly elderly, and with associated comorbidities.

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