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The use of Adriamycin and its derivatives in the treatment of prostatic cancer*

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Summary. Adriamycin and the other anthracyclines are amongst the most effective cytotoxic agents at the clinician's disposal. At least one of the reasons for their efficacy is the large number of mechanisms by which they can induce potentially lethal damage in a dividing malignant cell. Adriamycin and epirubicin are amongst the more effective agents in advanced hormone-independent prostate cancer. When given in full doses, they produce a reasonable number of objective as well as subjective responses, but the resultant toxicity precludes their use at high dose in many patients. In a number of well-documented studies, lower doses of these agents have yielded useful subjective responses with minimal toxicity.

Introduction

Prostatic cancer is a tumour of the elderly whose incidence is maximal during the eighth decade of life. In the majority of Western countries, some 70% of patients present with advanced local, or metastatic disease. In its early stages, prostate cancer may be curable by radical surgery and/or radiation therapy. Once it has advanced, however, treatment can only be palliative and is aimed at the relief of local and systemic symptoms.

Even in its advanced stages this disease remains sensitive to hormone manipulation. The hormonal influence on the growth of normal prostate cells is maintained in malignancy, with the cells being predominantly stimulated by testosterone and other androgens produced by the testicle and adrenal glands. The growth of these cells may also be directly influenced by two pituitary hormones: prolactin and growth hormone. Withdrawal of these hormones results in the arrest of prostatic cell multiplication in the majority of cancers.

MacNeal [10] has identified what is widely regarded as premalignant change in a number of experimental and clinical prostate cancers. The observed changes have led to the introduction of a concept for the development of clinical prostate cancer that is somewhat different from established carcinogenic principles. It seems that one of the earliest changes in prostatic cells that leads to malignancy is a lack of senescence. This essentially means that the cells are not dying as they normally do, and although the multiplication of cells at this stage may not be faster than normal, the lack of cell death results in a greater number of cells and, therefore to apparent new growth. Experimentally, these cells, which do not age normally, are also seen to be those that can escape the normal control mechanisms exerted by hormones and other growth factors. This observation suggests that as this lack of aging progresses, increasing numbers of cells at a given stage of growth will become relatively hormone-independent.

Failure of conventional therapy

Since 1943, a large number of hormonal manipulations have been used in an attempt to control the proliferation of prostate cancer. Over the course of the last 50 years, no single therapy has been proven more successful than orchiectomy in diminishing the overall mortality of patients with prostate cancer [7]. The European Organisation for Research and Treatment of Cancer (EORTC) and other organisations have performed a series of clinical trials, which have failed to demonstrate any significant advantage for anti-androgens alone, estrogens, progestogens or low-dose combinations of cytotoxic hormone preparations such as Estracyt and prednimustine. The results of many of these trials are well known. It is noteworthy that in studies that included patients with advanced local disease as well as metastatic disease, the median duration of survival was a little over 2 years, whereas in trials that were restricted to patients with metastases, survival was diminished, with at

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least 50% of the patients progressing or dying within 18 months. In some studies, total androgen blockade through the addition of a non-steroidal anti-androgen to orchiectomy or luteinising hormone-releasing hormone (LHRH) therapy has led to an increase in survival.

Biology of hormone escape

It has been shown by Labrie et al. [9] and other investigators that in an expanding tumour mass a number of clones of cells may be identified that respond to varying concentrations of testosterone or dihydrotestosterone.

Almost from the beginning of the growth there are probably one or more clones that are completely independent of androgen control. In a series of ingenious experiments, Coffey and Isaacs [7] have shown that there may be three different mechanisms for the development of hormone-independent cells. The first and most obvious one is the direct mutation of DNA. The second involves the possibility that the cell may adapt to a changing environment; in other words, as androgens are withdrawn by hormonal therapy, the cell learns to live in a low-androgen environment. The third possibility would be that hormone-independent cells are present from the start, albeit in comparatively small numbers, and become obvious only after the remainder of the tumour has been controlled by hormone manipulation or some other therapeutic modality. The latter concept fits well with the observed natural history of prostate cancer, particularly with the timing of apparent hormone relapse.

When the tumour is metastatic, the treatment of hormone-resistant cells may be accomplished only by chemo- or immunotherapy, and since the numbers of these cells are comparatively large, the latter treatment is most unlikely to be successful. As second-line therapy, both the completion of total androgen blockade in a patient who has previously been orchiectomised and the use of other hormonal manipulations have resulted in only short-term subjective responses.

Chemotherapy of hormone-independent prostate cancer

Since 1975, a number of chemotherapeutic agents have been tested in relapsed prostate cancer. The early ones such as procarbazine and hydroxyurea failed to produce a significant response. As reported by the Southeast Cancer Study Group in 1984, single-agent treatment with 5-fluorouracil appeared to offer some benefit according to National Prostatic Cancer Project (NPCP) criteria. In contradistinction to other urological tumours, cisplatin and methotrexate appear to be largely ineffective against relapsed prostatic cancer. Both the NPCP [11] and the EORTC [8] have carried out a series of studies using single-agent chemotherapy or a combination of chemo- and hormonal therapy, and the overall responses have generally been both small in number and short-lived. The combination preparation of estramustine, an oestrogen combined with a nitrogen mustard, has been shown to be reasonably effective when used at high doses, but it produces significant toxicity. In a recent phase III study carried out by the EORTC, the patients did no better on Estracyt than they did on single-agent mitomycin C, and in a heavily pretreated group of patients, neither agent appeared to improve the subjects' quality or quantity of life [12].

EORTC studies

Table 1 shows a summary of the phase II trials conducted by the EORTC in patients with advanced, measurable metastatic prostate cancer.

NPCP studies

The results of trials carried out by the NPCP are summarised in Table 2.

Use of anthracyclines and their derivatives in hormone-relapsed prostate cancer

Adriamycin and its derivatives are anthracyclines that have a fascinating series of properties unlike those of most other cytotoxic agents. It seems that these agents may inhibit cell growth and lead to cell death by exerting their activity not only at the cell membrane but also within the cell itself; moreover, it is almost certain that they are capable of dissociating the binding of DNA helices as well as breaking cross-links between nucleotides and proteins (Table 3). Since it is believed that one of the reasons why prostate-cancer cells continue to live involves inhibition of the intercellular enzymes that cause cell death, the possibility that anthracyclines can reverse this persistence by affecting the topoisomerases makes the use of these agents particularly interesting in the treatment of hormone-independent tumours.

A number of studies carried out in the United States have recently been summarised by Drago [4] in Catalonas' book on urological oncology. The studies, which were carried out and previously reported by Eagon and DeVyss, showed that as a single agent, Adriamycin appeared to be as effective as any other chemotherapeutic agent and considerably more effective than some of those tested in early investigations. One of the principle problems with Adria-

Table 1. Advanced measurable metastatic prostate cancer: screening of chemotherapeutic agents in EORTC phase II trials

Protocol	Closed	Number of patients
30763 – Procarbazine/ADM	June 1979	55
30799 – Vindesine	November 1981	40
30804 – MMC	March 1984	58
30841 – Epirubicin	October 1985	70
30852 – Methotrexate	April 1989	28
30884 – Epirubicin	–	2
Total number of patients studied		253

ADM, Adriamycin; MMC, mitomycin C

Table 2. Results of NPCP studies

Group	Protocol-dose mg/m^2)	Treatment	Number of patients	Partial regression (%)	Stable disease (%)	Progression (%)
I	100	5-FU	33	12	24	64
		CTX	41	7	39	54
		Standard	36	0	19	81
	300	CTX	35	0	26	74
		DTIC	55	4	24	72
		PCB	39	0	13	87
	700	CTX	12	0	50	50
		Methyl-CCNU	14	7	29	64
		Hydroxyurea	13	0	0	100
II	200	Estracyt	46	6	24	70
		Streptozotocin	38	0	32	68
		Standard	21	0	19	81
	400	Prednimustine	62	0	13	87
		Prednisolone + estracyt	54	2	11	87
	800	Estracyt	15	7	13	80
		VCR	14	0	7	93
		Estracyt + VCR	15	7	7	86
II	600	DES				
		DES + CTX				
		DES + Estracyt				
IV	500	DES or orchiectomy	23	22	43	35
		CTX + DES	18	17	78	6
		CTX + Estracyt	20	10	60	30

5-FU, 5-Fluorouracil; CTX, Cytoxan (cyclophosphamide); DTIC, dacarbazine; PCB, polychlorinated biphenyl; CCNU, lomustine; VCR, vincristine; DES, diethylstilbestrol

mycin itself is its toxicity profile. Naturally, patients with hormone-resistant prostate cancer are old and often frail with many associated chronic diseases. In particular, the incidence of cardiac disease is high, and it is obviously even higher in patients who receive stilbestrol or hormone preparations that cause cardiovascular damage. The high incidence of cardiac abnormalities following Adriamycin therapy, identified by Torti et al. [15], has persuaded many clinicians that the use of the parent compound Adriamycin is not suitable in this group of patients [15] (Table 4).

In the early 1980s, a number of authors obtained some beneficial results using *mini*-dose Adriamycin in the treatment of patients with advanced breast cancer. It appeared that an extremely low dose of this drug could produce a useful clinical response, resulting in only minimal toxicity and, particularly, in very few side effects on the myocardium. In 1985, Robinson et al. [13] described a small series of data collected by the Yorkshire Urological Cancer Research Group on patients with hormone-relapsed prostate cancer who had been treated weekly with Adriamycin at a dose of 10 mg/m^2 (Table 5). A useful subjective response was achieved in over 60% of the patients, and this response lasted for an average of 4 months. Very little toxicity was encountered, and the treatment was extremely well tolerated. One criticism of this and other similar series (Tables 6, 7) is that no proper placebo group was used, and it may well be that the weekly attendance of the patients at the clinic or ward was as beneficial as the agent itself.

Table 3. Actions of anthracyclines

1. At the cell membrane
2. DNA intercalation
3. DNA-protein link breakage
4. Topoisomerase inhibition

Table 4. Toxicity of Adriamycin[a]

1. Myocardial toxicity
2. Leukopenia
3. Gastrointestinal toxicity
4. Alopecia
5. Stomatitis

[a] From Torti et al. [15]

Table 5. Response to weekly treatment with Adriamycin at a low dose of 10 mg/m^2 [a]

Number of patients	16
Subjective response	68%
Duration of response	16/52 weeks

[a] From Robinson et al. [13]

Table 6. Response to weekly treatment with Adriamycin at a dose of 30 mg/m^2 [a]

25 patients	NPCP	EORTC
Partial response	84%	33%
Subjective response	67%	50%
Time to progression		23/52 weeks
Survival		41/52 weeks

[a] From Torti et al. [14]

Table 7. Response to weekly treatment with Adriamycin at a dose of 20 mg[a]

Number of patients	21
Subjective response	30%
Duration of response	20/52 weeks
Number of patients receiving alkaline or acid phosphatase	10/21

[a] From Fosså et al. [5]

Table 8. Response to weekly treatment with epirubicin at a dose of 30 mg/m^2 for 6/52 weeks[a]

Number of patients	8
Subjective response	100%
Partial response	50%

[a] From Francini et al. [6]

With the discovery of epirubicin (4-Epiadriamycin), the prospect of having access to an agent with good cytotoxic activity against prostate cancer that would produce only minimal cardiac toxicity was encouraging. Using full doses, Burk [2, 3] and Francini et al. [6] have shown that epirubicin has significant activity in patients who have relapsed on hormone therapy and that its activity is associated with a significant incidence of partial objective responses as judged by EORTC criteria (Tables 8, 9). Burk

Table 9. Response to weekly treatment with epirubicin at a dose of 25 mg/m^2 [a]

	EORTC
Number of patients	60
Partial response (12/52 weeks)	36%
↓Acid phosphatase	48%
Subjective response	ca. 80%
Survival:	
Partial response	50% at 24/12 weeks
Minor response	50% at 23/12 weeks

[a] From Burk et al. [3]

Table 10. Comparison of single-agent epirubicin treatment vs combination chemotherapy[a]

EPI, 25 mg/m^2 weekly	
vs	
5-FU/EPI/MMC,	3-week cycles
vs	
5-FU/ADR/MMC,	3-week cycles
(No benefit from combination therapy)	

[a] From Burk [1]
EPI, Epirubicin; 5-FU, 5-fluorouracil; MMC, mitomycin C; ADR, Adriamycin

Table 11. Response to weekly treatment with epirubicin at a dose of 12 mg[a]

Number of patients	33
Number of cycles	4–62
Partial response	12%
Subjective response	33%
Duration of response	12/52 weeks

[a] EORTC study 30841; from Jones et al. [8]

[1] explored the possibility of combining epirubicin with other cytotoxic agents and found that no actual benefit was obtained from any of the regimens tested (Table 10). This, of course, mirrors the American experience, in which the addition of other agents merely added to the toxicity without significantly improving the clinical response. Other workers have continued to give epirubicin at low doses, obtaining results similar to those reported by Robinson et al. [13] for Adriamycin (Table 11).

Discussion

Patients with hormone-relapsed prostate cancer are not easy to treat with any agents that produce significant toxicity. They are elderly, have chronic disease, particularly cardiac disease, and are therefore liable to suffer, possibly unnecessarily, from the side effects of cytotoxic treatment. As the majority of cytotoxic agents cannot be given in full doses to this group of patients, their efficacy is always seen to be low. If the biological findings of Coffey and Isaacs are correct, then, logically, since the presence of hormone-independent cells is identifiable as soon as the growth becomes clinically obvious, it would seem that cytotoxic agents should possibly be used at the outset, i.e. as soon as it has been decided that the tumour is not surgically curable. The EORTC GU Group is presently in the process of carrying out such a study; patients with poor prognostic factors, known to be associated with a high proportion of hormone-independent cells, are being treated with a combination of orchiectomy and the cytotoxic agent mitomycin C on diagnosis. The results of this study will not be available for another 2 years.

Since the management of metastatic prostate cancer is always palliative, that palliation must be seen to be effective, and further studies of cytotoxic and other potentially harmful treatments must include a proper assessment of the patients' quality of life as well as the usual objective and subjective evaluation of their response as compared with that of subjects undergoing placebo treatment. In two studies, the EORTC has attempted to do this, but difficulties in analysis of the data collected have led to some problems with the exact interpretation of the results.

In conclusion, there presently appears to be a need for the continued investigation of cytotoxic agents, particularly anthracyclines, in the management of hormone-independent prostate cancer. These investigations should properly be carried out in the context of clinical trials, and until a really useful response with minimal toxicity has been demonstrated, their use cannot be widely recommended. The administration of cytotoxic treatment during the early stage of this disease would seem to be a logical step. The use of mini-dose treatment with epirubicin continues to attract attention, but even at these low doses, toxicity may occur.

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