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ADJUVANT CYTOTOXIC CHEMOTHERAPY IN ASSOCIATION WITH RADICAL SURGERY OR RADICAL RADIATION TREATMENT IN PRESUMABLY LOCALIZED PROSTATIC CANCER

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Abstract

The potential benefit of adjuvant cytotoxic chemotherapy after radical surgical or radiation treatment of prostate cancer is discussed in the light of available reported studies. It is concluded that the effect of such treatment must still be regarded as uncertain and that further trials are needed.

Key words: Prostate cancer, adjuvant chemotherapy.

Virtually all authors agree that the treatment of prostatic cancer localized to the prostate gland (stage A2 and B) consists of radical prostatectomy or external radiotherapy. There has been a renewed interest in radical surgery since the improvement of the techniques allowing a considerable reduction in the risks of incontinence and preservation of the nervi erigentes, giving the patient a good chance of retaining his sexual potency. However, for surgery to have a real curative action, the disease must not have extended beyond the prostatic capsule.

It must be recognised that a certain number of cancers considered to be localized and treated as such by radical prostatectomy or 'definitive' radiotherapy are found, on histological examination of the resection specimen, to have extended beyond the prostatic capsule or to have invaded the seminal vesicles or, on preoperative or preradiotherapy 'staging' lymphadenectomy, to have invaded the lymph nodes.

The need for complementary treatment is obvious in these patients with stage C or D1 disease. Complementary radiotherapy of the prostatic and lymphatic bed can be proposed after surgery, or adjuvant endocrine treatment can be proposed in every case (according to various modalities: orchiectomy, antiandrogens, LHRH agonists, etc.).

Does adjuvant cytotoxic chemotherapy constitute a valid alternative? This is the subject of the present discussion.

Choice of adjuvant chemotherapy

The choice of the agent or agents to be used for adjuvant chemotherapy in prostatic cancer is particularly difficult. In fact, despite the large number of published series concerning chemotherapy for hormone-resistant metastatic prostatic cancer, no drug has demonstrated any remarkable efficacy or any superiority over other drugs, either as single-agent therapy or in combination with several drugs (1).

The occasional authors who have used and evaluated chemotherapy in this field have principally selected cyclophosphamide, which has the advantage of low toxicity and great reliability of use, and estramustine phosphate, although the hormonal component of the action of this drug interferes with the interpretation of the results.

Pilepich et al. (2) have tested a regimen consisting of doxorubicin cytoxan and cisplatin as an adjuvant to definitive radiotherapy in patients with high grade (Gleason score of 8–10), locally advanced carcinoma of the prostate limited to the pelvis. The evaluation was based on 9 patients. Although this regimen has been reported to produce a high rate of responses in disseminated disease and has not been associated with an increased incidence of

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radiation/chemotherapy toxicity in the irradiated pelvis, the effect of marrow suppression makes it unsuitable as adjuvant therapy.

Clinical experience—review of the literature

The clinical experience acquired at the present time based on a review of the literature is extremely limited. Very few series have been reported, corresponding to very small numbers of patients, and very few chemotherapeutic agents have been tested. Several study protocols are underway but no final conclusions are available.

The first experience with adjuvant cytotoxic chemotherapy over the last 10 years was reported in 1982 and 1983 by De Vere White et al. (3, 4) in patients with pathological stage D1 disease whose prostatic primary was treated with interstitial irradiation. One group, receiving adjuvant therapy consisting of cyclophosphamide and doxorubicin was compared to another group with no adjuvant therapy. Of the patients who received adjuvant chemotherapy 33% (4 out of 12) developed disease progression after an average follow-up of 37 months with a mean interval of recurrence of 15 months, compared with 48% (12 out of 25) of the patients not receiving adjuvant chemotherapy.

In a series, published in September 1989, of 60 patients treated in Memphis by external beam radiation therapy for carcinoma of the prostate between 1975 and 1984, Brausi & Soloway (5) gave adjuvant therapy to 22 patients; 11 received estramustine (600 mg/m^2 p.o. 3 times a day) and 11 received cyclophosphamide (1 g/m^2 i.v. every three weeks) after the completion of radiotherapy.

Adjuvant therapy in this study appeared to have no effect on preventing local or distant metastases in these patients treated with definitive irradiation. The failure rate in this group of patients receiving estramustine or cyclophosphamide was 50% compared with 26% of recurrences found in the population who did not receive therapy. This, according to the authors, can be explained by the high perecentage of stage D1 tumours (64%) observed in the first group. The mean time of progression for the few patients who received cyclophosphamide or estramustine was 19.6 months compared with 17.7 months observed in the other group (no significant statistical difference). There was no difference between the effect of estramustine and cyclophosphamide.

The conclusion of the authors is that in this limited series adjuvant therapy in addition to definitive radiation did not retard the progression of the disease. But the complications in the group receiving cyclophosphamide or estramustine were much greater (32%) than in those in the other group (5.2%).

Since 1976, Carter et al. (6) have adopted a surgical approach in the management of clinically localized prostatic adenocarcinoma, offering radical prostatectomy to all suitable candidates with clinical stage A2 or B lesions irrespective of tumor grade or pathological findings at lymphadenectomy. Of 108 patients treated between 1976 and 1984, 47 (44%) had unexpected pathological stage C or D1 disease.

The 31 patients with stage C disease received postoperative adjuvant radiation therapy (45 to 55 Gy). Actuarial 5- and 10-year disease-free survival rates were 92%, with a local recurrence rate of 3% and a distant recurrence rate of 6% at a mean follow-up of 5 years.

Of the 16 patients with pathological state D1, 4 received adjuvant external beam irradiation (45 to 60 Gy) alone, 5 adjuvant cytotoxic chemotherapy (cyclophosphamide) alone, and 7 both treatments. Actuarial 5- and 10-year disease-free survival rates were 86% with no local recurrence and a distant recurrence rate of 12% at a mean follow-up of 5 years. The detailed results are listed in the Table.

These remarkable results lead to the conclusion of the authors, that radical excision of the primary tumor and pelvic lymph nodes followed by early aggressive adjunctive therapy in pathological stages C or D1 disease provides excellent control and decreases or delays progression to distant metastases, resulting in prolonged disease-free survival.

In 1978, the NPCP launched two protocols evaluating adjuvant therapy following surgery (Protocol 900) or irradiation (Protocol 1000) for clinically localized prostate cancer.

All patients underwent staging pelvis lymphadenectomy. Following definitive treatment, patients were randomized to either:

- — cyclophosphamide (1 g/m^2 i.v. every 3 weeks for 2 years)
- — estramustine phostate (600 mg/m^2 p.o. daily 2 years)
- — or observation only.

Patient accession closed in 1985 and included 170 evaluable patients in Protocol 900, and 233 evaluable patients in Protocol 1000. To our knowledge the final results have not yet been reported from this study. However, some partial results have been presented at the annual meeting of the American Society of Clinical Oncology, in Atlanta, in May 1988 (7).

In Protocol 1000 the progression-free survival (PFS) for stage D1 patients was significantly better for estramustine adjuvant (median of 35.3 months) compared to no treatment (median of 19.7 months). For all patients in this procotol, the PFS was significantly greater in the estramustine group (median 46.9 months) compared to that in the cyclophosphamide group (median of 31.9 months).

Median PFS and survival were generally better for patients in Protocol 900 compared to 1000, regardless of adjuvant therapy, reflecting the greater proportion of lower pathologic stage patients in the surgically treated group.

The partial conclusion is that estramustine adjuvant

Table

Results of local and/or systemic adjuvant theraphy in pathological stage D1 disease following radical prostatectomy (ref. 6)

Adjuvant therapy	Patients n	Mean months follow-up (range)	N° Local recurrence n	Distant recurrence n (%)	Alive without evidence of disease (%)
All stage D1	16	61 (36–132)	0	2 (12)	82
Radiotherapy	4	90 (36–132)	0	0	100
Chemotherapy	5	60 (36–75)	0	0	80
Chemotherapy + radiotherapy	7	46 (36–50)	0	2 (28)	72

treatment is of benefit to prostate cancer patients with pelvic node involvement receiving irradiation as definitive treatment.

Discussion

An evaluation of the utility and efficacy of adjuvant chemotherapy after radical treatment by prostatectomy or radiotherapy of localized prostatic cancer can be based on very little data at the present time:

- The inconclusive results of the already old series by De Vere White et al. (3, 4) are difficult to interpret due to the risk of inadequate local control by simple interstitial irradiation.
- The study by Brausi & Soloway (5) did not demonstrate any action of adjuvant chemotherapy on disease progression and duration of survival, and the complication rate was much higher in the group receiving chemotherapy.
- The results of the series reported by Carter et al. (6) are quite remarkable, attributed by the authors to the 'aggressive' adjuvant therapy used in stages of disease extending beyond the capsule. However, although radiotherapy of the prostatic and lymphatic bed after surgery is probably effective, evaluation of adjuvant chemotherapy was actually only based on 12 cases, including 7 cases receiving also radiotherapy, and the role of chemotherapy in the improvement of the results remain problematical.
- Lastly, the NPCP protocols have not yet been fully analysed. They suggest some action of estramustine after primary radiotherapy of the prostatic tumour. But is not this action the result of the hormonal effect of this drug rather than its chemical effect? On the other hand, nor all the D1 stage patients have the same prognosis, and in these protocols there is a significantly better progression-free survival rate in patients with less than 20% of removed nodes involved with prostatic cancer compared with those with more than 20% involvement (8).

Conclusion

We are obliged to conclude that, at the present time, we do not have any evidence of the efficacy of adjuvant chemotherapy after radical prostatectomy or 'definitive' radiotherapy. The definitive value of such adjuvant treatment must be assesssed in terms of a reduction in the number of patients subsequently developing metastases: no such demonstration is as yet available.

We also know, from our experience with other tumours, that an effective adjuvant chemotherapy must include a drug or a combination of drugs, previously shown to give massive or at least obvious response in advanced metastatic cancer.

No such chemotherapeutic agents active against prostatic cancer are available at the present time, which is demonstrated by the diversity of response rates reported after similar protocols used in metastatic cancers. The response criteria themselves are not universal and vary according to the different research organizations (NPCP, ECOG, EORTC).

Under these conditions, it must be difficult to demonstate a complementary benefit of chemotherapy following initial radical treatment (radical prostatectomy or irradiation). This demonstration will require many more protocols with much longer follow-up than those available at the present time. Chemotherapy has also to be compared with the various modalities of endocrine therapy, the efficacy of which has been demonstrated for a long time.

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