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Chemotherapy of Bladder Tumours

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Intravesical Chemotherapy of Multiple Papillary Tumours

According to several reports, various drugs can produce total or partial regression of multiple papillary tumours.

Thiotepa. This drug has been widely employed but can give rise to severe side-effects and even death. The drug can be absorbed from the bladder and pass into the circulation, with subsequent bone marrow toxicity. The rate of absorption varies with several factors, such as dose, concentration, urinary pH, etc. Absorption is greatly increased after loop resection or fulguration, and in cases of cystitis or vesico-ureteric reflux. It is greater in anaplastic carcinoma than in well-differentiated transitional-cell tumours. In some instances, especially if given shortly after a TUR (9), as much as 96% of the administered dose can be reabsorbed. The results are not uniform and response rates varying from 24 to 100% have been reported by different authors.

Other drugs, such as VM-26, peptichemio and adriamycin, give a variable degree of success.

According to Riddle and Wallace (12), local treatment with triethylene glycol diglyceridyl ether (Epodyl) is followed by a high response rate (50% complete and 42.5% partial remissions after 12 weeks of treatment. These results need to be confirmed by other workers. It is suggested in particular, that a controlled randomised trial should be initiated, to compare the effects of Epodyl to those of other treatments. This drug is commercially available only in few European countries.

It has been pointed out that topical treatment of bladder tumours, whatever drug is employed, can be very effective in some patients, but useless in other apparently identical cases. The explanation is still unknown. In vitro studies, for testing the sensitivity of bladder tumours to antiproliferative drugs, have not yet proven their practical value (10).

Apart from the choice of the drugs, the optimal dosage and the best modalities of treatment still need to be defined. It is also uncertain whether new procedures, such as hydraulic distension or hyperthermia may yield similar or even better results.

It should be stressed, however, that intravesical chemotherapy or any other conservative treatment should be attempted before performing total cystectomy for a clinically benign condition such as multiple papillomatosis.

Intravesical Chemotherapy of Carcinoma-in-Situ

Very little is known about the value of topical chemotherapy in carcinoma-in-situ of the urinary bladder. In theory, this condition (which gives rise to infiltrating carcinoma in a high percentage of cases) should respond to local chemotherapy even better than well differentiated transitional cell tumours. If the

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assumption that topical chemotherapy acts by inhibition of cell proliferation is correct, the treatment should be more effective on atypical neoplastic cells than on cells that show little difference from those of the normal mucosa. On the contrary, preliminary reports seem to indicate that carcinoma-in-situ is poorly responsive to most chemoterapeutic agents except adriamycin.

Postoperative Chemoprophylaxis of T1 Papillary Tumours

This topic has been discussed in previous publications (5, 6). Several authors believe that postoperative chemotherapy is of value in preventing recurrences following TUR or other conservative treatments. The mechanism of action of intravesical prophylactic treatment with chemotherapeutic agents may be either the prevention of tumour cell implantation at the time of surgery or an antiproliferative effect on established tumour foci that are too small to be seen cystoscopically. If the first assumption is correct, then treatment, given during or immediately after surgery, should be not only practical but also effective. Some advantage from adding anti-cancer drugs to the fluids employed for bladder irrigation during or after TUR has been shown (4). No toxic effects from absorption were ever observed, due to the low concentration of the active drugs. In a retrospective, non randomised study, a 60% recurrence rate in untreated patients was observed. This was reduced to 23.4% after long-term postoperative treatment and 36.3% following bladder irrigation with anti-cancer agents.

In a recent randomised trial, Burnand et al. (1) showed that the instillation of 90 mg thiotepa in 100 ml sterile water immediately after TUR or fulguration is effective. Only 1 of the 32 untreated patients remained recurrence free, as opposed to 8 patients in the group of 19 treated with thiotepa. This difference is statistically significant.

Prolonged intravesical chemoprophylaxis is employed by most workers. It has been shown that recurrences often occur after stopping the treatment. It is advocated, therefore, that the treatment should continue for one or two years. The drugs are the same as those employed for topical chemotherapy of established tumours. Many of them have proven effective. A controlled prospective randomised trial was activated over a year ago by the E.O.R.T.C. urological group (13). The disease-free interval, the degree of malignancy of recurrence and the 5-year survival rates will be compared for T1 bladder tumours after TUR only, and after TUR followed by local thiotepa (30 mg) or teniposide (VM-26:50 mg) in 30 ml water. Both drugs are to be retained for 1 hour, and administered at weekly intervals for a month and then at monthly intervals for 1 year.

Patients in whom repeated vesical catherisation is unpractical can be given oral prophylactic treatment with drugs displaying a high rate of urinary excretion, such as hydroxyurea or procarbazine. It seems, however, that the efficacy of oral treatment tends to fade with time. Of 94 patients given longterm postoperative treatment in a non-randomised study (4), a 16% recurrence was observed in patients treated intravesically and 25% in patients given oral drugs, as opposed to a 60% recurrence rate in a similar group of 40 patients given no treatment.

Systemic Chemotherapy of Deeply Infiltrating, Recurrent or Metastatic Carcinoma

Chemotherapy is the only possible treatment when metastases are present or previous cystectomy and radiotherapy have failed. A survey of published data was reported in 1973 (6). It was stressed that variable rates of transient objective regressions were reported in several series, but that the number of treated cases was relatively small. No controlled trials were reported except that of Prout et al. on 5-FU versus placebo (11). No permanent cure due to chemotherapy alone had ever been observed.

In a personal series prior to 1971 (4), a number of chemotherapeutic agents were tested with variable degree of success. A 47.8% regression rate was obtained with mitomycin C, but only 73.3% of regressions were complete or greater than 50%. A higher percentage of remissions and improvement of survival rate were obtained in patients treated with radiotherapy and 5-FU in comparison to radiotherapy alone. These results however were not confirmed by a subsequent randomised study by Edland et al. (2).

Few drugs have been adequately tested. Even 5-FU results in regression rates varying from 0 to 75% in different series. Similarly, the regression rate in patients treated with adriamycin varies from 0 to 57% from one study to another. Peptichemio, cyclophosphamide, hydroxyurea, VM-26 (6, 7) and other drugs have also been tried on a small number of cases with encouraging results.

In a later study (8), the E.O.R.T.C. urological group obtained objective regression in 16.1% of patients treated with adriamycin,

26.2% with VM-26 and 33.3% with bleomycin. The groups were not identical, and no clear-cut superiority of one drug over the others could be demonstrated. The results were better when high doses of the drugs could be employed.

In another pilot study (3) on the association of adriamycin and 5-FU (50 mg/m^2 of adriamycin and 500 mg/m^2 of 5-FU i.v. at intervals of 21 days), the E.O.R.T.C. urological group obtained apparently better results. Out of 52 evaluated cases, 4 complete regressions were observed. Three patients were free of all evidence of disease at 7,13 and 16 months. Objective regression (total or greater than 50%) was obtained in 40% of cases. The side effects were mild and the treatment was performed on ambulatory patients in most cases.

In conclusion, as pointed out by Staquet, (14) there is little scientific basis for a rational programme of chemotherapy for bladder cancer. There is not only a lack of randomised controlled trials, but most of the available drugs have not been tested even in uncontrolled studies. However, the possibility of obtaining even temporary regression and palliation should not be underestimated, when no other effective treatment is available.

A new randomised trial has been designed and already activated by the E.O.R.T.C. urological group, to compare the efficacy to adriamycin with that of cyclophosphamide and adriamycin with 5-FU.

Adjuvant Chemotherapy, in Addition to Surgery or Irradiation

This is a new, promising field, but little has been achieved so far. Chemotherapy may be of value if given preoperatively or postoperatively or in association with radiotherapy. A controlled trial of treatment following pre-operative radiotherapy and cystectomy comparing chemotherapy (Adriamycin + 5-FU) with immunotherapy and including a control group has been recently designed by the E.O.R.T.C. urological group.

Intra-arterial Chemotherapy

Some promising data have been published concerning intra-arterial chemotherapy of locally inoperable bladder cancer. Surgical placement of the catheters is necessary.

Experience is limited and there is considerable escape of drugs into the systemic circulation. The value of the procedure needs to be established.

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