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Bladder cancer chemotherapy studies supported by the National Bladder Cancer Project

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Summary. *The collaborative group chemotherapy studies of the National Bladder Cancer Project are summarized with regard to intravesical and systemic agents. The necessity for longitudinal observations and data collection in all cases of bladder cancer, and not just those receiving chemotherapy, is also stressed.*

Introduction

For the past 10 years much of the research on urinary bladder cancer done under the aegis of the National Cancer Institute has been coordinated and funded by the National Bladder Cancer Project. As one of four NCI organ site research programs, the NBCP has attempted to focus the attention of both basic and clinical scientists on the preclinical as well as the clinical course of the disease in bladder cancer patients. Research has been directed at cause and prevention, as well as at the development and implementation of diagnostic and therapeutic strategies, and we have also been concerned with encouraging studies of the psychosocial concerns of those who have, or who might develop, bladder cancer.

The results of research sponsored by the NBCP have been communicated at meetings and published in the biomedical literature, but in addition we have encouraged direct interaction of those working on different aspects of the bladder cancer problem at the NBCP Annual Workshops. To keep urologists and other clinicians informed about new methods of patient management, we held the First National Bladder Cancer Conference in 1976, and in early January, 1983, we will sponsor the Second National Bladder Cancer Conference in conjunction with the American Urological Association. We have also tried to develop closer ties with bladder cancer research programs in other countries, and we believe the resulting improved interchange of ideas and personnel has been mutually beneficial.

The general organization and research approach of the NBCP has been discussed elsewhere, and an annual summary of all research activities funded through the project is available from Project Headquarters at St Vincent Hospital. There are currently several studies in progress dealing with the use of chemotherapeutic agents in laboratory or clinical settings. In this report, however, I will confine myself to a summary of the results of the cooperative, multi-disciplinary, multi-institutional chemotherapy studies conducted by Clinical Collaborative Group A (CCGA) of the National Bladder Cancer Project.

Collaborative Group A presently includes the following institutions and principal investigators contributing bladder cancer case material:

Institution	Urologist/Principal Investigator
Johns Hopkins	Michael Droller
Massachusetts General Hospital	George R. Prout, Jr
Medical College of Virginia	Warren W. Koontz, Jr
Roswell Park Memorial Institute	Zew Wajsman
Rush-Presbyterian St. Lukes'	Malachi Flanagan
University of California at San Diego	Joseph Schmidt
University of Iowa	Stefan Loening
University of Oregon	Harper Pearse
University of Tennessee	Mark Soloway
University of Wisconsin	Kenneth Cummings
Virginia Mason Medical Center	George Brannen

In addition, statistical, pathology and administrative services are provided by the following organizations and principal investigators:

Organization	Principal Investigators
Statistical Coordinating Center (Georgetown University)	Sidney J. Cutler
Central Pathology Laboratory (St. Vincent Hospital, Worcester)	Gilbert H. Friedell
Administrative Center (Massachusetts General Hospital)	George R. Prout, Jr, Chairman

In order to participate in CCGA studies a Collaborating Institution must show the active participation of the Urology, Pathology, Radiotherapy, and Medical Oncology Departments at that Institution. Within each institution there must be good communication between the individuals representing

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these disciplines. In addition, the individuals representing the four disciplines at each Collaborating Institution meet together as Speciality Subcommittees in Urology, Pathology, Radiotherapy, and Medical Oncology. Finally, there is at least one representative of each speciality on each of the several protocol committees. The latter are responsible for planning, implementing, monitoring, and reporting the clinical studies which the group undertakes.

The group is in its ninth year of existence and the participants have learned much about the conduct of successful clinical trials. One of the important lessons the group learned early in its existence was that all – or as close to 'all' as possible – cases of bladder cancer at each institution must be registered, and even if the urologist does not wish the particular patient to receive the experimental agent the descriptive features for each case, e.g., stage, location, histologic type and grade, and duration of the tumor must be given. This is necessary to establish the size and characteristics of the *denominator,* or pool of cases, from which those cases involved in therapeutic trials will be drawn. The latter will of course be the *numerator.* Such information will not only permit us to see what proportion of the total number of bladder cancer patients will be included in any given treatment protocol, but will permit us to compare the bladder cancer patient population in one institution with that in another. Both of these comparisons are very important and necessary for inter-institutional comparisons of therapeutic results.

Another important factor in the conduct of a successful multi-institutional therapy study is the availability of some means of assuring comparability of case material, i.e., assuring that when tumors of a given histological type or stage are discussed there is general agreement that in fact all of the tumors *really are* the same type and stage. That is, there is an urgent need for a good quality control mechanism to be built into the group's structure at its very beginning. Moreover, the quality control element must be developed and implemented not only for the evaluation of histopathologic and cytologic specimens, but also for the assessment of clinical features, e.g., number, location, and size of bladder tumors seen at cystoscopy by the urologist. Finally, the overall quality of data entered into the record keeping system(s) of the clinical study must be constantly monitored.

In CCGA these quality control functions are performed by the Central Pathology Laboratory, the Administrative Center, and the Statistical Coordinating Center. The successful collection of 'good data' by CCGA, and our ability to draw valid conclusions from our investigations, reflect a significant investment of time, human energy, and money in these activities.

Having now given you some idea of the basis for the clinical trials conducted by Group A, I will summarize briefly our completed and current chemotherapy studies. I will focus first on the therapy of disease in the bladder, then discuss our chemotherapeutic studies of metastatic bladder cancer.

Protocol I A.
Surveillance of patients with carcinoma of the bladder

Purpose of study. To categorize and classify, at all Collaborating Institutions, patients with bladder carcinoma throughout the course of the treated disease. From this population, selected patients may be entered into protocols evaluating alternative methods of clinical management, including treatment or secondary prevention but not limited to therapy. That is, methods of patient diagnosis, follow-up, or evaluation of response might be the objects of subsequent studies.

Current status. This protocol is in both follow-up and accessioning phases. Some 3,400 patients have been enrolled under this protocol – or its predecessors – during the past 7 years.

Conclusions. These continuing longitudinal investigations of bladder cancer patients are yielding important histopathological and cytopathologic information about the most appropriate methods and criteria for classifying patients for treatment and for assessing and classifying their responses to therapy [1–6, 8]. This information has been incorporated in patient management protocols as it has become available.

Protocol 3.
Effect of intravesical instillation of antineoplastic agents on superficial primary bladder carcinomas and the recurrence rate of these carcinomas in adult patients

Purpose. This study was designed to test both the ablative or therapeutic effect of thio-TEPA on papillary T_a or T_1 stage carcinomas of the bladder and the prophylactic effect of thio-TEPA in the prevention of tumor recurrence.

Conclusions. In the therapeutic study 47% of 95 patients were free of disease after two courses of treatment. The 30-mg dose was as effective as the 60-mg dose. Within this group of cases neither the grade nor the stage of the papillary tumors was associated with response to treatment.

The prophylaxis study included 93 patients, of whom 20 were given the 30-mg dose of thio-TEPA, 23 were given the 60-mg dose, and 47 patients were put in the control group. The disease-free interval was significantly longer in the prophylaxis group than in the control group following the initial TUR. As in the previous thio-TEPA study, the 30-mg dose was as effective as the 60-mg dose. The disease-free interval appeared to be shorter in patients with positive cytology in bladder washings, but this difference between prophylaxis and control groups was not statistically significant. It was noteworthy that in the small group of patients successfully treated with thio-TEPA as a tumor-ablative measure but randomized to the control group in the prophylaxis study, 60% were free of disease at 12 months [7].

Protocol 6.
Phase-I/II study of 13 cis-retinoic acid as an agent for preventing recurrent superficial papillary bladder tumors

Purpose of study. To assess the 6-month recurrence rate in patients at high risk for recurrence who are given this agent PO.

Status of study. Terminated after entry of 22 patients.

Conclusions. Of 18 patients who received the drug and whose data were available for analysis, the agent failed to prevent recurrence in 15. The 6-month recurrence rate was 63%, a

figure comparable to the 57%–70% recurrence rate in historical controls. Moreover, toxicity was a definite problem. Because of this and the apparent lack of chemo-prevention, this protocol was terminated.

Protocol 10.
Phase-III randomized study to compare the ablative effect of thio-TEPA with that of mitomycin C in cases of superficial bladder cancer

Purpose. To study the gross ablative effect of these agents given as intravesical instillations, to compare the toxic effects of the agents, and to compare the disease-free intervals in the two groups.

Status of study. Case accrual is proceeding on schedule. Thio-TEPA is instilled at 30 mg per week for 8 weeks. Mitomycin is instilled at 40 mg per week for 8 weeks.

Protocol 11.
Phase-III randomized study comparing the effectiveness of a single dose of thio-TEPA vs an initial dose followed by a maintainance regimen of thio-TEPA in superficial bladder cancer patients at high risk for developing recurrent tumors

Purpose. To compare the results of 'one-shot' thio-TEPA therapy with those of a 2-year maintainance program of therapy with thio-TEPA.

Status of study. Case accrual is proceeding on schedule.

Protocol 7. Phase-III randomized clinical trial of systemic adjuvant chemotherapy following preoperative radiation and cystectomy in patients with invasive bladder carcinoma

Purpose. To assess the value of adjuvant chemotherapy (*cis*-diamminochloroplatinum II) in controlling systemic disease.

Status of study. Cases are still being accessioned to this protocol. It is evident, however, that a more suitable drug would have significantly lower toxicity, and thus be more acceptable to the elderly, usually quite ill, population of patients with bladder cancer. No analysis of results is available at this time.

Protocol 8.
Phase-I trial of cis-diamine dichloroplatinum II (CDDP) combined with small-field pelvic radiation therapy

Purpose. To test the advisability of offering patients who are not candidates for cystectomy a therapeutic regimen combining an effective chemotherapeutic agent with full-dose radiation therapy.

Status of study. Accession of patients has been completed but data have not yet been analysed.

Protocol 9.
Phase-II master protocol for the evaluation of new systemic chemotherapeutic agents for the treatment of advanced bladder cancer

Purpose. To evaluate AMSA as the first of such new agents, following which FAM combination therapy will be initiated.

Status of study. Sufficient cases treated with AMSA have been accessioned but analysis of data is not available yet. The FAM (5-fluorouracil, Adriamycin, and mitomycin C) therapy regimen is being instituted in this group of patients.

Protocol 5.
Phase-III study of cis-diamine dichloroplatinum II (CDDP) vs CDDP plus cyclophosphamide in patients with advanced bladder cancer

Purpose. To evaluate therapy of metastatic disease with CDDP.

Status of study. Completed.

Conclusions. There were 10 objective responders (20%), including five with complete responses, among the 50 evaluable patients who received CDDP alone, and seven responders (11.9%), including with complete responses, among the 59 receiving combination therapy. The treatment arms did not differ significantly in percentage of responses.

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