Chemotherapy and Urological Malignancy

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Series Editor's Foreword

Chemotherapy for malignant disease has brought about many rapid and often spectacular improvements in the survival rate of some groups of patients. Yet enthusiasm for these successes has, in part, been offset by the problems in evaluating responses to treatment and by the disappointment of failing to check the progress of still so many other tumours. These reactions will be no surprise to the medical historian but perhaps the expectations from scientific progress nowadays sometimes demand more than can reasonably be expected.

Another expectation is that any review of chemotherapy is completely up to date, even prophetic. Such is the expansion of the subject that new drugs and trial results are continually being reported but it is this very mass of information that creates its own problems and makes many clinicians despair of finding a balanced judgement on all of this information.

This was the challenge accepted by Professor Spiers. He then gathered together a group of colleagues who are amongst the acknowledged leaders in the field of chemotherapy for urological tumours, all of whom have made important contributions to this subject. However, each chapter is not merely a record of the author's experience but encompasses an assessment of past and present practice as well as perspectives in diagnosis and management. Almost all chapters include reference to published work up to and including 1981.

This book systematically reviews the role of chemotherapy for each of the anatomical sites that comprise the genito-urinary tract, including the adrenal gland. The successes and failures, rewards and frustrations that are part of the progress of chemotherapy are all encompassed by this group of tumours. Even where the progress has been dismal, it is important to appreciate the efforts that have been made and the problems that have beset many a study. The contributors have not avoided these issues and their presentation of all their experiences adds only to the appreciation of their successes.

Clinical trials have become the basis for all chemotherapeutic studies. Uncontrolled use of these powerful and often dangerous drugs is to be deplored. Collaborative studies both in the US and Europe are described in the hope that many readers will be encouraged not only to

see that their patients receive the optimum treatment but also to participate in trials where the issues are far from resolved. Even where a treatment protocol has been well established, it will be evident that much of the success lies in careful patient monitoring. In this book, the contributors have carefully presented each subject so that the reader can judge what is the role of chemotherapy as part of overall management, what has become accepted clinical practice and what needs further evaluation.

Professor Spiers has met easily the challenge presented to him: this book offers the clinician a clear, concise and current summation of the state of the art and science of chemotherapy for urological tumours. The reader will readily appreciate the expertise with which the book has been prepared and will welcome the guidance offered herein.

Edinburgh, April 1982 Geoffrey Chisholm

Preface

The practising urologist spends much time as a specialized surgical oncologist. Although a minority of his patients have cancers, their needs for primary treatment, follow-up, reoperation, reconstructive and diversionary procedures, and continuing care, require from him a major commitment. In some other cancers, ongoing care can be assumed by the medical oncologist or the radiotherapist, but in urological malignancies, continuing surgical interventions are frequently necessary for the proper management of patients.

The most common urological cancers, those of the prostate and of the urothelium, are usually diagnosed by the urologist, who is then responsible for staging procedures and for the initial surgical management. There is an increasing tendency to involve the radiotherapist and the medical oncologist at an early stage in treatment planning, even in cases where primary surgical cure is likely. This admirable tendency has sprung from the willingness of urologists to support a multidisciplinary team approach to cancer. Its benefits include not only better care for patients, but also a widening of the experience of his colleagues in the other disciplines, who in the past were apt to see urological cancers only in their advanced stages.

The late complications of urological cancers, and the sequelae of treatment, often require the urologist's skills. His role as a surgical oncologist does not of course end there. As a medical oncologist, I find that the urology team is one of my most frequent allies, and many of my patients with tumors of nonurologic origin causing ureteric obstruction, have had extra months or years of useful life as a result of successful urinary diversion.

The aim of this book is to review the present status of chemotherapy for the common, and also the rare, urological cancers. For the urologist who may not himself administer chemotherapy, the aim is to provide an indication of what his medical oncologist colleague can offer. For the medical oncologist, we have endeavoured to provide both practical advice on current therapy and an indication of possible future progress. Of necessity, the authors have not confined themselves to a discussion of chemotherapy alone. Each chapter makes reference to diagnosis, pathology, staging, and natural history, and usually to surgical treatment and radiotherapy. This is a hallmark of progress:

chemotherapy for cancers cannot be considered in vacuo, but must be seen in the context of the extent and bulk of tumor, and of the contributions that can be made by other treatments. This multimodality approach to the treatment of cancer is emphasized throughout the book: in Wilms' tumor and in testicular cancer it has been dramatically successful, and it can reasonably be hoped to improve the outcome in commoner and more obdurate tumors such as bladder and prostatic cancer.

The subject matter is arranged on an obvious anatomical scheme beginning with the adrenal and proceeding downward to the testes. Drs. Zeffren and Yagoda have assembled the most comprehensive account extant of the drug therapy of adrenal cancer. Mitotane, the drug most widely used for this tumor, is unique among the cytoxic agents both for its peculiar specificity and its dual mechanism of action, antagonizing hormone synthesis and also inducing tumor cell necrosis. The development of better assays for both the drug and for the hormonal products of adrenal tumors promises to improve the management of this disease. The authors point out — and the theme recurs in other chapters — that the difficulties in the assessment of tumor response and the lack of adequately standardized criteria for reporting responses continue to impede progress in chemotherapy.

The two following chapters contrast sharply. Carcinoma of the kidney is remarkably resistant to cytotoxic drugs, and response to hormonal manipulations is uncommon, incomplete, usually of brief duration, and has not convincingly been shown to improve the length or quality of life. It is notable that recent studies, with proper evaluation of results, show the lowest response rates. There is a need for continuing cooperative studies to evaluate the many old and new drugs that have not undergone adequate trial in this neoplasm. In Wilms' tumor, Dr. Kumar and his colleagues tell a story of considerable achievement. In about forty years, the cure rate has risen from around 15% to about 90%. These impressive results are brought about by the successful application of multidisciplinary teamwork to the management of each patient. In Wilms' tumor, therapy has reached the encouraging stage where the overall intensity of the treatment actually is being reduced in some cases, because the risk of tumor recurrence is becoming less than the hazards of overtreatment.

Dr. Kasimis discusses the chemotherapy of the rarer tumors of the urothelium. His careful review underlines the paucity of data and the need for cooperative group studies to provide information that is unlikely to be gathered by a single institution. The results of surgery or radiotherapy are unsatisfactory, particularly for advanced tumors of the upper urothelial tract, and it cannot safely be assumed that agents with some activity against bladder cancer will be effective in pelvic, ureteric, or urethral tumors.

Superficial tumors of the urinary bladder possess many special features. Their tendency to recurrence and to multiplicity presents special problems to the surgeon who wishes to avoid cystectomy but does not wish to jeopardize the patients' survival. The accessibility of the bladder to repeated inspection and to endoscopic manipulations makes possible follow-up observation and treatment which is not feasible for the majority of visceral tumors. Topical therapy of early

tumors, by the intravesical instillation of a variety of cytotoxic agents, is a logical and important approach to superficial bladder cancers. Dr. Soloway provides an outstanding review of the current status of intravesical therapy, and makes clear the many problems in this field which can be resolved only by carefully planned prospective clinical studies. Not least of the problems is the considerable expense of repeated cytoscopic examinations and the high cost of several of the cytotoxic agents employed. Such factors make it even more important that the value of intravesical therapy be critically assessed before it is too widely adopted.

Although advanced cancer of the bladder is more responsive to systemic chemotherapy than is renal cancer, existing chemotherapy regimens are rarely curative. Dr. Yagoda considers several agents, notably cisplatin, to be clinically useful, and there is evidence of prolongation of life for approximately a year in patients who respond to therapy. The role of adjuvant chemotherapy after apparently complete surgical resection of bladder cancers is being studied in randomized controlled trials. The need for effective adjuvant chemotherapy is undoubted, as over 50% of patients who are treated with radiotherapy followed by radical cystectomy die within 5 years from recurrent cancer.

Drs. Torti and Carter review the therapy of cancer of the prostate. A complex staging system now in use may enable better identification of poor prognostic groups. Although cancer of the prostate is common, there is surprisingly little reliable information on the effectiveness of cytotoxic drugs. In part this may be due to unwillingness to administer aggressive therapy to elderly men who frequently suffer from multiple medical illnesses. Undoubtedly, the widespread use of estrogens has for many years retarded research with other forms of drug therapy. Patients who receive cytotoxic drugs only after a prolonged trial of estrogens generally are in poor condition, with a high tumor burden, and are unlikely to achieve useful remissions with available agents. At least six drugs appear to have significant activity in prostatic cancer, but there is insufficient evidence to support their use in combinations, other than in the setting of a formal clinical study. The limitations of orchiectomy and the morbidity associated with the use of estrogens should prompt further trials of chemotherapy early in the course of metastatic cancer of the prostate.

Penile cancer is of interest to the chemotherapist because of its sometimes dramatic responsiveness to bleomycin, a sensitivity which unfortunately is not shared by other squamous cell cancers. Drs. Sklaroff and Yagoda consider bleomycin, methotrexate, and cisplatin to have useful activity in penile cancer; combined drug regimens are not yet adequately evaluated, and the value of adjuvant chemotherapy after surgery remains to be established. Very few institutions have sufficient patients to mount their own trials in this uncommon tumor, and cooperative multicenter studies are needed.

Drs. Einhorn and Williams review the management of testicular cancer. In the past decade there have been truly exciting advances in this field. The cure rate for disseminated testicular cancer has risen from approximately 10% to 70% with a combination of multiple-drug chemotherapy and, in some cases, surgical excision of residual disease.

Testicular cancer is a model of how progress can be made in cancer therapy. There have been improvements in the pathological characterization of the tumors, and lymphography and abdominal computerized axial tomography have greatly improved the staging of disease and the planning of therapy. Exploitation of the tumor markers, alpha fetoprotein and beta-chain human chorionic gonadotrophin, has enabled the monitoring of responses to therapy and the detection of residual disease with a refinement available in very few other tumors. The application of accurate staging, serial marker studies, and combinations of surgery and multiple-agent chemotherapy, has drastically improved the prognosis of this important tumor of young men.

Modern clinical studies in cancer frequently ask difficult questions and seek statistically secure answers. When relatively small differences in outcome are sought, large numbers of patients must be studied, and cooperative ventures involving many hospitals are essential if answers are to be provided in reasonably short periods of time. In the United States, cooperative groups have a long and distinguished history, but most do not extend across national boundaries. In Europe, the EORTC is an outstanding example of international cooperation in clinical cancer research. The work of the EORTC in urological cancers has been accorded a special chapter, because its emphasis, and in some instances its philosophy, often differ significantly from practice in the United States. Thus in testicular cancer, the approach to retroperitoneal nodes seems quite different on the two sides of the Atlantic, and it is uncertain if the 'correct' course of action has yet been defined. Perchance it is waiting to be picked up in mid-ocean.

It should give considerable satisfaction to the practising urologist that two urological cancers — Wilms' tumor and testicular cancer — are now repeatedly cited as examples of the success of modern cancer therapy, and as vindications of the multimodality approach to the management of tumors. Tomorrow's challenge is to lengthen the list.

Albany, April 1982

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Contents

Chapter 1

Chemotherapy of Adrenal Cortical Carcinoma

J. Zeffren and A. Yagoda

The evaluation of anti-neoplastic agents in the treatment of patients with carcinoma of the adrenal cortex has been relatively limited since the incidence of this tumor is only 0.2/100,000. However, the propensity for adrenal cortical carcinoma to excrete hormones has led to unique groups of drugs which produce significant palliation of bothersome and life-threatening endocrinologically induced symptoms. Cushing's syndrome, virilization, feminization, sexual precocity, gynecomastia, hirsutism and hypertension, which are more frequently recognized in females and young children, are secondary to the overproduction of various class II (glucocorticoid) and III (17-ketosteroid) steroids. Malignant adrenal cell carcinoma, which is of mesodermal origin, does not excrete 'unusual steroids', rather they simply 'reflect inefficient use of the normal steroid precursors by the neoplasm and increased excretion of the metabolites normally present in only trace amounts' (Lipsett et al. 1963). For example, it has been estimated that the excretion rate of 17-hydroxycorticoids (17-OH) averages 1 mg/g of normal adrenal tissue compared to only 0.1–0.2 mg/g of tumor (Lipsett et al. 1963). In addition, such tumors are not totally independent of normal hormonal control since some investigators have found modulation of steroid secretion with ACTH (adrenocorticotropin) and dexamethasone administration (Rayfield et al. 1971; Bulger and Correa 1977). Thus, a large tumor burden is generally required before significant endocrinologic signs and symptoms appear which is in marked contrast to the efficient steroid production by small non-malignant adrenal cortical adenomas.

Typically, it is secondary effects of excessive steroid production that bring the patient to medical attention, which explains why in almost half the cases a palpable mass is discovered on initial physical examination (Lipsett et al. 1963; Hutter and Kayhoe 1966a). In a report from Memorial Sloan-Kettering Cancer Center, tumor size varied from 4 to 40 cm in diameter and only 1 of 34 cases showed gross evidence of encapsulation (Huvos et al. 1970). In another study (Lipsett et al. 1963) 20 of 38 patients had a tumor weighing >500 g. Local tumor extension is frequent as shown in a series of 127 cases in which 65% had tumor involvement of adjacent structures (Hutter and Kayhoe 1966a). Metastases are more frequently found in lung, liver, lymph nodes and intra-abdominally, and less commonly in skin, brain and osseous

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sites. Large masses, particularly abdominal metastases, tend to have areas of central necrosis.

Adrenal cortical carcinomas are divided into two groups — functioning and non-functioning — on a clinical and/or a biochemical basis. However, with modern biochemical techniques more tumors have been found to secrete into the blood various steroid metabolites not previously detected in the analysis of steroids excreted in urine. Such recent findings hinder an accurate assessment of the efficacy of some drugs in earlier trials.

Surgical resection is the treatment of choice for localized tumors. Even in selected patients with metastases, particularly those with Cushing's syndrome, significant palliation and possible prolongation of life can be achieved with surgery. However, palliation is short-lived in the majority of cases which present with metastases. In spite of a report by Steward et al. (1974) who noted beneficial effects with radiation therapy, most studies find these tumors relatively radioresistant. In addition, there is no evidence that post-operative irradiation decreases the incidence of metastases (Lipsett et al. 1963).

In late 1948 toxicologic studies in dogs described necrosis of the liver and adrenal cortex with the insecticide DDD, a chemical congener of DDT. The ortho, para isomer, o,p′-DDD (1, 1 dichloro 2 (o-chlorophenyl)-2-(p-chlorophenyl) ethane) was discovered to cause focal degeneration of the zona fasciculata and zona reticularis in the canine adrenal and eventually, o,p′-DDD was brought into clinical trials specifically for the treatment of metastatic tumors of the adrenal cortex.

In humans, 11-beta hydroxylation of adrenal steroids is blocked by daily doses of 0.5–3.0 g of o,p′-DDD and adrenal atrophy with glucocorticoid, and mineralocorticoid deficiency occurs with doses exceeding 3.0 g (Hogan et al. 1978). After an oral dose of o,p′-DDD approximately 40% is absorbed. Maximum plasma concentration is attained by 3–5 h and tissue (particularly in fat) equilibrium by 12 h. While 10% is excreted in urine as various metabolites, 20%–30% is stored in tissues as dichloroethene and acetic acid metabolites for 3.5–8.5+ months. Storage of o,p′DDD metabolites in fat is probably very prolonged since trace levels in plasma have been found 18 months after cessation of therapy (Hogan et al. 1978).

o,p′-DDD affects hepatic microsomes as shown by a change in the metabolism of barbiturates. Of clinical importance is the observation by Wortsman and Soler (1977) of an antagonism between spironolactones (e.g. Aldactone) and o,p′-DDD. In dogs, pretreatment with a spironolactone prevents o,p′-DDD-induced adrenocortical tissue necrosis. In humans, o,p′-DDD is ineffective, when given with spironolactone, in decreasing serum steroid levels and in ameliorating the symptoms of Cushing's syndrome.

The efficacy of o,p′-DDD has been established in a series of reports (Lipsett et al. 1963; Hutter and Kayhoe 1966a, 1966b; Lubitz et al. 1973) between 1959 and 1973 by the National Cancer Institute from data filed by over 200 physicians who administered the drug to patients with adrenal cortical carcinoma. In 1960, Bergenstal et al. described objective tumor regression and a decrease in abnormally elevated urinary steroid excretion in 7 of 18 patients given 8–10 g p.o. for 4–8 weeks. In the report by Hutter and Kayhoe (1966b) on 138 patients o,p′-DDD produced clinical responses in 35%. Tumor regression was obtained in 34% of 59 evaluable cases, but as noted by the authors 'exact measurements were rarely reported, a clear indication by the investigator of definite regression in measurable disease was accepted as evidence of response'. Reduction in elevated urinary 17-ketosteroids and 17-hydroxy or ketogenic steroids was found in 72% of 62 cases with response graded as good (30%–50% reduction of the metabolite measured) in 3% and 5%, respectively. In females, prolongation of life was found in o,p′-DDD responders who had docu-

mented tumor regression. Non-responders and patients who showed only a decrease in steroid excretion had a similar duration of survival. Age, site of metastases or the induction of toxic side effects with o,p′-DDD did not influence response. In patients with measurable lesions, although the response rate was 20% (2/10) for non-functioning tumors vs. 35% (12/34) for functioning tumors, the difference was not statistically significant ($p > 0.5$). In 115 patients treated between 1965 and 1969 Lubitz et al. (1973) noted tumor regression in 61% of 75 cases and a decrease in elevated steroid excretion in 85% of 61 cases. Increased survival occurred primarily in responders who had measurable tumor. Some patients who relapsed after chemotherapy was discontinued because of toxicity experienced a second objective remission with resumption of o,p′-DDD. The reason for the higher response rate in the summary of trials reported by Lubitz et al. (1973) compared with Hutter and Kayhoe (1966b) could be explained by patient selection (i.e. a shorter interval between diagnosis and treatment), different histologic types (Huvos et al. 1970) varied drug dosages and durations of therapy, assessment of changes in tumor volume (by 95 different physicians) and more accurate biochemical tests coupled with a response criterion of *only* a greater than 30% reduction in urinary steroid excretion, equal to the 'fair' category in the series of Hutter and Kayhoe (1966b).

The longest duration of survival has been reported by Becker and Schumacher (1975) and Exelby (1975) who describe two patients alive at 4 and 7 years, and one patient alive at 6 years, respectively, after beginning o,p′-DDD therapy. However, there are two negative reports by Hajjer et al. (1975) and Bulger and Correa (1977). In the former study, a small group of patients obtained no benefit with the use of o,p′-DDD as an adjunct to surgery or as a single therapy, while in the latter, no responses were observed in five patients, but 'in all but one patient the drug was discontinued in less than 1 month because of poor patient tolerance'.

Between 1949 and 1977 twelve patients at Memorial Sloan-Kettering Cancer Center were given o,p′-DDD alone. Doses, schedules and the duration of drug administration varied. Of nine adequately treated patients one obtained complete remission and one a minor response. An additional patient who received o,p′-DDD combined with a 4-month course of 5-fluorouracil has remained in complete remission for 3+ years.

The onset of biochemical response to daily administration of o,p′-DDD is rapid; 50% by day 17 in one series (Lubitz et al. 1973), and 49% within 21 days and 37% between 21–30 days in another series (Hutter and Kayhoe 1966b). Measurable tumor regression occurs later, 4–6 weeks (range 1½–28 weeks) with a mean of 8–9 weeks. Occasionally, responses can be very delayed with initial improvement observed biochemically at 2.5 months and on physical examination at 19 months (Lubitz et al. 1973). Thus, the definition of an adequate trial of o,p′-DDD should be 4–6 weeks for biochemical parameters and 12 weeks for measurable lesions (Exelby 1975).

The proper dose, schedule and duration of therapy of o,p′-DDD is still undetermined. Since the major dose-limiting toxicities of o,p′-DDD are gastrointestinal disturbances — anorexia, nausea, vomiting and diarrhea and central nervous system abnormalities – depression ('gloom and doom'), lethargy, somnolence, vertigo and confusion, many patients refuse maintenance therapy. Hutter and Kayhoe (1966b) noted responses biochemically in 29 of 31 patients to doses of ≤ 10 g daily (average 8.5 g) and tumor regression in 15 patients with an average dose of 8.1 g daily. One patient who relapsed after a 20-month remission responded again when o,p′-DDD was increased from 4 to 8 g daily. Although response may have been dose-dependent in one or two patients, Hutter and Kayhoe (1966b) concluded that 'undesirable side effects of o,p′-DDD are not required for response'. Lubitz et al. (1973) cautioned against interrupting o,p′-DDD therapy.