VOL 15, NO 1

JANUARY 1997

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company

JOURNAL OF CLINICAL ONCOLOGY
The Official Journal of the American Society of Clinical Oncology

Journal of Clinical Oncology (ISSN 0732-183X) is published monthly by W.B. Saunders Company. Corporate and Editorial Offices: The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Accounting and Circulation Offices: W.B. Saunders Company, Periodicals Dept., 6277 Sea Harbor Dr, Orlando, FL 32887-4800. Periodicals postage is paid at Orlando, FL 32862, and additional mailing offices.

POSTMASTER: Send change of address to *Journal of Clinical Oncology,* c/o W.B. Saunders Company, Periodicals Department, 6277 Sea Harbor Dr, Orlando, FL 32887-4800.

Editorial correspondence should be addressed to George P. Canellos, MD, *Journal of Clinical Oncology,* 850 Boylston St, Suite 301A, Chestnut Hill, MA 02167. Telephone: (617) 739-8909; FAX (617) 739-8541. Email: whippend@jco.asco.org. Internet: http://www.jcojournal.org/

American Society of Clinical Oncology-related questions should be addressed to ASCO, 225 Reinekers Lane, Suite 650, Alexandria, VA 22314. Telephone: (703) 299-0150; FAX: (703) 299-1044.

Correspondence regarding subscriptions or change of address should be addressed to W.B. Saunders Company, Periodicals Department, 6277 Sea Harbor Dr, Orlando, FL 32887-4800.

Change of address notices, including both the old and new addresses of the subscriber, should be sent at least one month in advance.

Customer Service and Subscription information: 1-800-654-2452.

Yearly subscription rates: United States and possessions: individual, $233.00; institution, $299.00; single issue, $30.00. All other countries: individual, $304.00; institution, $356.00; single issue, $30.00. For all areas outside the United States and possessions, there is no additional charge for surface delivery. For air mail delivery, add $72.00. Student and resident: United States and possessions: $83.00; all other countries: $96.00. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription are on a prorated basis. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. *1996 bound volume price:* $95.00; international customers, please add $25.00 for postage. To purchase a 1996 bound volume, customer must be a subscriber for 1996. *Cumulative Index (1983-1989) price:* $95.00; international customers, please add $2.25 for surface delivery, or $8.00 for air mail. Prices are subject to change without notice. *Checks* should be made payable to W.B. Saunders Company and sent to *Journal of Clinical Oncology,* W.B. Saunders Company, Periodicals Department, PO Box 628239, Orlando, FL 32862-8239.

Agents for the United Kingdom, Ireland, and Europe: Harcourt Brace & Company, Ltd, 24-28 Oval Rd, London NW1 7DX, England. Agents for Australia and New Zealand: Harcourt Brace & Company Australia, Pty. Limited, 30-52 Smidmore St (Locked Bag 16), Marrickville, NSW 2204, Australia. Agents for Japan and Korea: Harcourt Brace & Company Japan, Inc, Ichibancho Central Bldg., 22-1 Ichibancho, Chiyoda-Ku, Tokyo 102, Japan.

Other correspondence (copyediting, production) should be addressed to W.B. Saunders Company, Periodicals Department, The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399.

Advertising representative: Cunningham Associates, 180 Old Tappan Rd, Old Tappan, NJ 07675; telephone 1-201-767-4170; fax 1-201-767-8065.

W.B. Saunders Company **Philadelphia, PA**

A Division of Harcourt Brace & Company

REVIEW ARTICLE

Second-Line Hormonal Therapy for Advanced Prostate Cancer: A Shifting Paradigm

By Eric J. Small and Nicholas J. Vogelzang

Purpose: To discuss the evolution of new concepts in the use of second-line hormonal therapy for patients with progressive prostate cancer despite androgen deprivation.

Design: Pertinent contemporary prostate-specific antigen (PSA)-based reports of the utility of secondary hormonal maneuvers after treatment with combined androgen blockade (CAB) were reviewed.

Results: The use of PSA as an end point in hormone-refractory prostate cancer (HRPC) trials is more widely accepted, but still remains somewhat controversial. Using PSA as an end point, it is clear that a variety of secondary hormonal maneuvers can result in responses. Antiandrogen withdrawal is efficacious in approximately 20% of patients and can be observed with a variety of antiandrogens, including flutamide, bicalutamide, and megestrol acetate. A variety of regimens, including megestrol, bicalutamide, glucocorticoids, aminoglutethimide, and ketoconazole, retain activity (14% to 75% PSA response proportion) even in patients who have failed to respond to CAB and flutamide withdrawal.

Conclusion: Once CAB (suppression of gonadal and adrenal androgen) is undertaken, further hormonal maneuvers remain efficacious in some patients with progressive prostate cancer. Antiandrogen withdrawal is now a mandatory maneuver before proceeding to other regimens. It is clear that certain patients will continue to respond to hormonal maneuvers even after antiandrogen withdrawal. An understanding of the molecular basis of these responses may result in the development of a more targeted therapy in the future.

J Clin Oncol 15:382-388.

PROSTATE CANCER is the most common malignancy in men, and in 1996, will account for more than 41,000 deaths in the United States.[1] Unfortunately, no hormonal therapy is capable of producing durable responses in any but a small minority of patients with metastatic prostate cancer. The median duration of response to androgen deprivation is approximately 18 months.[2] The development of antiandrogens such as flutamide and bicalutamide for use in combination with gonadal androgen ablation (combined androgen blockade [CAB]) appears to have improved survival in some patients.[3,4] However, all advanced prostate cancer patients treated with androgen deprivation eventually develop progressive hormone-insensitive disease, as evidenced by increasing prostate-specific antigen (PSA) levels, progressive disease on imaging studies, or progression of symptoms, usually pain. Virtually all prostate cancer fatalities are due to the development of hormone-refractory prostate cancer (HRPC). The approach to advanced prostate cancer patients who have failed to respond to therapy with androgen deprivation has undergone a significant and fundamental transformation over the last 2 to 3 years and is the subject of this report. This changing paradigm is in part a consequence of the development of novel therapeutic interventions for this group of patients, but is in no small part also due to the redefinition of HRPC.

END POINTS IN ADVANCED PROSTATE CANCER TRIALS

An evolution in the understanding of the end points that are used to describe the effect of treatment of HRPC patients has contributed in part to the development of this new paradigm. Several reviews have commented on the difficulty in drawing conclusions from the literature regarding the most appropriate therapies for hormone-resistant prostate cancer because of the differing criteria for study inclusion and response assessment.[5,6] The earliest clinical trials for advanced prostate cancer reported objective or subjective responses, although criteria for quantification of these results were not specified. Subsequently, the National Prostate Cancer Project (NPCP) established rigid response criteria. Since most patients who entered these trials had clinically progressive disease, stabilization of disease, presumably as a consequence of therapy, was considered an objective response. However, these criteria have been roundly criticized, and most investigators today do not use either the stable disease category or the NPCP criteria.[5,6] Some investigators have advocated

From the Department of Medicine, and the Urologic Oncology Program, University of California, San Francisco, and Mt Zion Cancer Center, San Francisco, CA; and Department of Medicine, University of Chicago, Chicago, IL.

Submitted March 6, 1996; accepted June 17, 1996.

Address reprint requests to Eric J. Small, MD, Urologic Oncology Program, University of California, San Francisco/Mt Zion Cancer Center, 2356 Sutter St, 5th Floor, San Francisco, CA 94115; Email eric_small@QUICKMAIL.UCSF.edu.

0732-183X/97/1501-0020$3.00/0

inclusion in clinical trials only of patients with measurable disease as a means to determine true response proportions. However, this is an impractical approach, since 80% to 90% of patients with HRPC do not have measurable disease. There is also disagreement as to whether patients with bidimensionally measurable disease represent a subset of patients with a worse prognosis.[7]

More recently, a decline in PSA level has been advocated as an intermediate marker of response, and a surrogate marker for survival in patients with HRPC.[8,9] While it seems clear that a greater than 50% (or in some series, 75%) decrease in PSA level appears to define a group of patients with improved survival, controversy remains as to the validity of decreased PSA as a surrogate marker of response or survival in patients treated with suramin.[10] Prospective validation of the percent decline in PSA level, as well as duration of PSA decline, as a variable predictive of outcome (ie, survival) is warranted. Furthermore, it should be noted that novel therapeutic agents, eg, immune-modulating or differentiating agents, and possibly even suramin, cannot be assumed to have a similar impact on PSA as more conventional cytotoxic agents.

Despite growing sophistication with the use of PSA as a predictive outcome variable, in one sense, we have come a full circle in assessing responses to therapy for advanced prostate cancer, in that patient-derived (ie, subjective) measures of clinical benefit have been recognized as reasonable (and in fact, critically important) end points. For example, a recent report that compared prednisone alone versus prednisone plus mitoxantrone failed to demonstrate a survival advantage for the chemotherapy arm, but demonstrated a dramatic improvement in quality of life (QOL) when mitoxantrone was included.[11] It is clear that future evaluations of therapy for HRPC must, in some fashion, measure changes in quality of life or pain, in addition to more conventional measures of response. However, the utility of many of these measures may be limited by the fact that an increasing reliance on PSA-defined disease progression has resulted in the treatment of more and more asymptomatic HRPC patients in whom no discernible changes in QOL would be anticipated.

THE OLD PARADIGM

An understanding of the adrenal contribution to the total testosterone pool,[2] coupled with the observation that clinical responses occur in men with relapsed prostatic carcinoma after castration when an antiandrogen is added,[12] have suggested that adrenal androgens provide continued stimulus to target cells still responsive to androgens. This hypothesis prompted several randomized trials in the late 1980s that compared CAB (the addition of an antiandrogen to the interruption of testicular androgen production) versus testicular androgen deprivation alone.[4] The largest reported series to date is the National Cancer Institute Intergroup study, which was initiated in 1985.[3] This was a double-blind, placebo-controlled trial in which 603 patients with stage D2 prostate carcinoma were randomized to receive leuprolide acetate alone versus leuprolide acetate plus flutamide. Time to progression (16.5 months *v* 13.9 months), as well as overall survival (35.6 months *v* 28.3 months), was superior in the combination therapy arm. Of interest, the superiority of combined therapy over leuprolide alone was most apparent in patients who had been prospectively stratified into a good-performance/minimal-disease category. These patients experienced a greater than 20-month survival advantage when treated with combined therapy. An important point to be made about this trial is that it was, by design, a crossover trial that allowed patients with progressive disease who had been on the placebo arm to then add flutamide to their regimen. In essence, this trial showed that immediate CAB was preferable to the delayed addition of an antiandrogen on progression.

While several other randomized trials have also shown a survival advantage to CAB, enthusiasm for this approach has been tempered by the fact that several smaller, yet moderately sized trials, as well as a meta-analysis, have failed to show an advantage to this approach.[4] Whether individual physicians are convinced of the utility of initial CAB, it is fair to say that either initial CAB or the late addition of an antiandrogen after progression after gonadal androgen ablation[12,13] has become the standard of care in the United States for patients with advanced prostate cancer.

Until recently, second-line hormonal therapy for HRPC had been used in the setting of an attempt to suppress adrenal androgen production in a patient who had not yet undergone total androgen blockade (ie, delayed total androgen blockade). This approach was based on the belief that the development of progressive disease reflected the capacity of certain clones of cells to grow in the presence of only minute concentrations of androgens, and that disease regression could be achieved by targeting previously untreated sources of androgenic stimulation. This was accomplished with ketoconazole, aminoglutethimide, or antiandrogens, such as megestrol acetate, flutamide, or bicalutamide. Ketoconazole and aminoglutethimide block steroidogenesis by inhibiting the conversion of cholesterol to pregnenolone. Thus, they are potent inhibitors of adrenal steroid production, including adrenal androgens, and replacement doses of hydrocortisone are required. Overall, objective partial responses have been

reported in 9% (aminoglutethimide) and 16% (ketoconazole) of patients, with stable disease (NPCP criteria) in 23% and 30%, respectively.[14] The role of patient selection in virtually all of these trials cannot be overstated: most were conducted before an understanding of the role of CAB, and virtually all of these patients had not undergone prior adrenal androgen deprivation.

Similarly, megestrol acetate (Megace, Bristol-Myers Squibb Company, Princeton, NJ) appears to have activity in HRPC by inhibiting release of luteinizing hormone (LH), blockade of the androgen receptor, and inhibition of 5-α-reductase. Some investigators suggest that it may be cytotoxic at high doses. Response proportions of approximately 40% have been reported, but again, these reports have all predated the more widespread use of CAB.[14] Other hormonal maneuvers that have been reported to have antitumor activity in HRPC patients not yet treated with CAB include glucocorticoids, high-dose estrogens, and antiestrogens. High-dose estrogens suppress pituitary gonadotrophins, compete for the androgen receptor, and may have a direct cytotoxic effect.

Glucocorticoids result in a medical adrenalectomy, with resulting decreased adrenal androgen production. A recent review of published clinical trials of patients who had progressed after primary hormone treatment, and whose subsequent treatment included glucocorticoids, reported a wide range of response proportions (0% to 66%). Of 19 trials reviewed, five included flutamide as one of the prior hormone therapies, but only one prospectively controlled for the potential contribution of flutamide withdrawal.[15] The diversity of response and entry criteria makes it impossible to draw generic conclusions about the utility of corticosteroids for the treatment of HRPC. While both objective and symptomatic improvements can be achieved with these approaches, their efficacy in patients who have already been treated with an antiandrogen is not known.

The interest generated by recent reports of a new generation of agents for the treatment of HRPC, including suramin[16-18] and estramustine-based regimens,[19-21] resulted in the recommendation that second-line hormonal therapy be reserved for patients who were not eligible for or declined therapy with investigational agents.[14,22] These recommendations have been bolstered by the perception held by some investigators that secondary hormonal maneuvers, particularly those aimed at adrenal androgen deprivation, while of utility in patients who were being treated only with gonadal androgen deprivation, were unlikely to be efficacious for patients already on CAB.

THE NEW PARADIGM

The recommendations described are being reevaluated as it becomes clear that HRPC is a heterogeneous disease, with varying degrees of retained hormonal sensitivity. The sentinel report that resulted in a fundamental restructuring of the way in which HRPC is conceptualized was published by Kelley et al[23] in 1993. A follow-up study of this report and two subsequent confirmatory studies have described the benefits of the discontinuation of flutamide in patients whose metastatic prostate cancer had become hormone-refractory.[24-26] This syndrome has been termed the ''antiandrogen withdrawal syndrome.'' These reports included a total of 139 patients (Table 1). Overall, approximately 20% of patients with progressive (hormone-refractory) prostate cancer treated with CAB had a significant decrease in serum PSA level when flutamide

Table 1. Summary Data of Antiandrogen Withdrawal

Variable	First Author			Total
	Scher[24]	Figg[26]	Small[25]	
Total no. of patients	36	21	82	139
Median age (years)	68	66 (mean)	71	70.1
Median start PSA (ng/mL)	103	NS	46	N/A
Prior concomitant flutamide therapy	25 (69%)	NS	57 (70%)	82
Prior nonconcomitant flutamide therapy	11 (31%)	NS	25 (30%)	36
Overall PSA response proportion	10/35 (29%)	7/21 (33%)	12/82 (15%)	29/138 (21%)
Median duration of responses (months)	5	3.7+	3.5	N/A
Response proportion in patients with prior concomitant flutamide therapy	10/25 (40%)	NS	8/57 (14%)	18/82 (22%)
Response proportion in patients with prior nonconcomitant flutamide therapy	0/11 (0%)	NS	4/25 (16%)	4/36 (11%)
Median duration of prior flutamide therapy in responders (months)	18	28.3	21	N/A
Median duration of prior flutamide therapy in nonresponders (months)	13	18.7	12	N/A

NOTE. Concomitant flutamide is defined as the simultaneous use of an LHRH agonist or orchiectomy along with flutamide (CAB). Nonconcomitant flutamide therapy is defined as monotherapy with an LHRH agonist or orchiectomy with the late addition of flutamide at progression, or as monotherapy with flutamide with or without the later addition of LHRH agonist or orchiectomy.

Abbreviations: N/A, aggregate median data could not be determined from available data; NS, not specified.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.