Progress in prostate cancer

Padraig Warde, MB; Mary K. Gospodarowicz, MD

Prostate cancer has now overtaken lung cancer as the most commonly diagnosed cancer in Canadian men, of whom 1 in 9 will eventually develop prostate cancer and 1 in 27 will die of the disease. The incidence of prostate cancer has doubled since 1969. Although it is frequently referred to as an indolent disease, prostate cancer is the second most common cause of death due to cancer in Canada (4100 deaths in 1997).

In the past 2 decades considerable progress has been made in the diagnosis and treatment of prostate cancer. Prostate-specific antigen (PSA) has proved to be one of the best tumour markers available to oncologists. Important therapeutic advances include the introduction of nerve-sparing radical prostatectomy, the development of high-precision radiation techniques to protect normal tissues and the availability of treatment with luteinizing hormone releasing hormone (LHRH) agonists as an alternative to orchidectomy. More recently, the development of effective chemotherapy for tumours resistant to hormonal therapy was reported by Tannock and associates.[1] In this Canadian study, treatment with mitoxantrone and prednisone significantly improved quality of life when compared with treatment with prednisone alone.

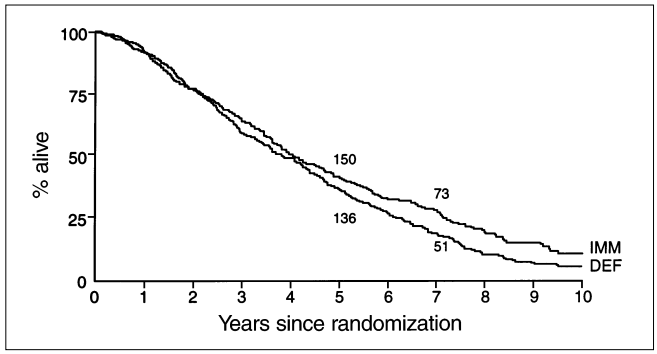
Against this background, we review the results of 3 phase III clinical trials published in 1997[2–4] that will clearly have an important impact on clinical practice.

Radiation therapy has generally been considered the treatment of choice for locally advanced (stage T3–T4) prostate cancer. Over the past decade, findings from a number of studies of neoadjuvant (i.e., given before definitive local therapy) and adjuvant hormonal therapy have suggested that hormonal therapy and radiation therapy in combination produced better results than treatment with radiation alone. However, the question of timing remained unanswered: the accepted standard was to defer hormonal therapy until relapse rather than to introduce it early in the course of the disease.

This July, Bolla and colleagues reported the results of a study of adjuvant hormonal therapy in stage T3 prostate cancer treated with radiation.[2] This trial, conducted by the Radiotherapy Group of the European Organization for Research on the Treatment of Cancer, randomly assigned 415 patients to receive external-beam radiation therapy alone or radiation therapy with 3 years of therapy with an LHRH agonist. For a median follow-up period of 45 months, the actuarial overall survival at 5 years was 79% (95% confidence interval [CI] 72% to 86%) in the combined therapy group as compared with 62% (95% CI 52% to 72%) in the radiation therapy group (p = 0.001). Improvement was also seen in clinical disease-free survival and local control. The 5-year PSA progression-free rate was 81% in the combined therapy group as compared with 43% in the radiation therapy group.

This trial confirmed the superiority of combined hormonal and radiation therapy in locally advanced disease. The benefit of radical radiation therapy in locally advanced prostate cancer is currently being assessed in a National Cancer Institute of Canada Clinical Trials Group study (PR3), in which patients are randomly assigned to receive either radiation therapy with hormonal therapy or hormonal therapy alone, with radiation therapy being reserved for local progression.

Hormonal therapy has been known to be beneficial since it was pioneered by Huggins and Hodge in 1941. However, the optimal timing for the introduction of hormones has been controversial. The usual practice has been to treat patients with symptomatic locally advanced or metastatic disease immediately and to defer hormonal ther-



Overall survival in 469 patients treated with immediate hormonal therapy (IMM) and 465 with deferred hormonal therapy. Numbers within graph are actual numbers alive at 5 and 7 years. Reproduced from Medical Research Council Working Party Investigators Group[3] by permission of Blackwell Science Ltd., Oxford, UK.

apy in asymptomatic patients to preserve sexual function. The Medical Research Council of the United Kingdom Prostate Cancer Working Party Investigators Group conducted a prospective randomized trial comparing immediate hormonal therapy with deferred therapy in patients with locally advanced or metastatic disease.[3] They observed a statistically significant improvement in overall survival in the immediate therapy group (see figure). The greatest benefit of immediate therapy was seen in patients with no evidence of distant metastases. Pathologic fracture, spinal-cord compression, ureteric obstruction and the development of extraskeletal metastases were twice as common in patients whose hormonal therapy was deferred.

The data from this study support early hormonal therapy for patients with prostate cancer. However, the benefits of early (and likely prolonged) hormonal therapy must be weighed against the deleterious effects of androgen ablation, which include loss of libido, fatigue and changes in bone mass. Further randomized trials are needed to define the optimal timing and delivery schedules of hormonal intervention; the assessment of the impact of therapy on quality of life should be an integral part of such studies.

After surgical castration with bilateral orchidectomy, circulating levels of androgens are still noted, because 5% to 10% of the total pool of circulating androgens are produced by the adrenal glands. The possible role of these adrenal androgens in the progression of prostate cancer is controversial. It has been suggested that the persistence of measurable dihydrotestosterone in the prostate (with relatively high intracellular levels) is due to the continued conversion of adrenal androgen precursors to testosterone and subsequently to dihydrotestosterone in the prostatic cells. Hence, the addition of antiandrogens that prevent androgens from being active at the target site should enhance the efficacy of primary androgen ablation by medical or surgical castration.

Since the early reports by Labrie and colleagues[4] of improved results with total androgen blockade, there has been ongoing controversy regarding the possible benefits of this approach. Numerous trials, often with small sample sizes, have given contradictory results. Earlier this year the Southwest Oncology Group reported the results of a study in which 1387 patients were randomly assigned treatment with bilateral orchidectomy and either a placebo or flutamide.[5] No difference in progression-free or overall survival was found between the 2 groups. In addition, no benefit was seen in patients with small-volume metastatic disease, who previously were thought to benefit most from the addition of antiandrogen therapy. These results indicate that there is no benefit to total androgen blockade in patients treated with orchidectomy. Although the controversy continues, it appears unlikely that this therapy has much impact on the survival of patients with metastatic disease.

These important clinical trials have substantially improved our understanding of the role of hormonal therapy in prostate cancer. However, in most patients prostate cancer eventually becomes refractory to hormonal therapy, and a major research effort is needed to improve our understanding of the mechanisms of hormone resistance. New therapeutic approaches are necessary, and it is essential that these be tested in well designed randomized clinical trials before being introduced into clinical practice. Only careful groundwork in clinical trials can prevent another impasse like the 15-year controversy over the efficacy of total androgen blockade.

The results from the European and UK studies indicate that the early introduction of hormonal therapy may improve survival. The European study gives us reason for cautious optimism that combined radiation therapy and hormonal therapy may lead to an improved cure rate in patients with locally advanced disease. The importance of randomized clinical trials in guiding our therapeutic approach to prostate cancer cannot be overemphasized. The studies reviewed here demonstrate that large phase III trials are feasible and can be conducted successfully by cooperative groups. However, only a few randomized trials now in progress are addressing the first-order controversies in this disease. For example, in patients with localized and locally advanced disease, is radical treatment superior to less intrusive strategies such as watchful waiting, especially in patients with well-differentiated tumours? Other trials are addressing the role of adjuvant hormonal therapy in localized disease, the possible advantages of intermittent hormonal therapy, and the role of high-precision radiation therapy. These studies will likely change the way patients with prostate cancer are managed and are essential if we are to move forward in dealing with this disease.

References

1. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-64.
2. Bolla M, Gonzales D, Warde P, Dubois J, Mirimanoff R, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295-300.
3. Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br J Urol* 1997;79:235-46.
4. Labrie F, Dupont A, Belanger A, Cusan L, et al. New hormonal therapy in prostatic carcinoma: combined treatment with LHRH agonist and an antiandrogen. *Clin Invest Med* 1982;5:267-75.
5. Eisenberger M, Crawford ED, McLeod D, Loehrer P, Wilding G, Blumenstein B. A comparison of bilateral orchidectomy with or without flutamide in stage D2 prostate cancer [abstract]. *Proc Asco* 1997;16:3.

Drs. Warde and Gospodarowicz are with the Department of Radiation Oncology, University of Toronto, and Princess Margaret Comprehensive Cancer Centre, Toronto, Ont.