Timing Therapy in Patients with Prostate Cancer

Studer UE, Hauri D, Hanselmann S, et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: results of the randomized trial SAKK 08/88. J Clin Oncol 2004;22:4109–18.

Study Overview

Objective. To compare immediate hormonal therapy (IT) with deferred treatment (DT) in patients diagnosed with prostate cancer who did not undergo local treatment.

Design. Randomized prospective trial with an intention-to-treat analysis.

Setting and participants. Between 1988 and 1992, asymptomatic patients diagnosed with prostate cancer (any stage) were enrolled into this Swiss multicenter trial. Patients were ineligible or unwilling to undergo radical prostatectomy or radiation therapy. Orchiectomy was performed ≤ 1 month after randomization in the IT group and in the DT group at the onset of symptoms from disease progression or when the patient was at risk for disease-related complications. Rising prostate-specific antigen (PSA) levels, new "hot spots," or soft-tissue metastases on study did not warrant DT as long as patients remained asymptomatic. After IT or DT, additional treatment was administered if patients experienced pain or if therapy was necessary to prevent pathologic fractures. After the second progression, management was left to the treating physician.

Main outcome measure. Overall survival.

Main results. 197 patients (median age, 76 years) were randomized to immediate or deferred orchiectomy at the time of symptomatic progression. The groups were well-matched in terms of baseline parameters. 67% had T3–4 tumors, 20% had nodal involvement, and 23% had metastases. 42% of patients in the DT arm did not undergo orchiectomy—92% of whom died from causes other than prostate cancer. DT was started after a median of 3.2 years. The time from random assignment to the first appearance of symptoms requiring additional treatment after immediate or deferred orchiectomy did not differ substantially between groups (P = 0.86). Increased PSA values, pain, hot spots, and voiding symptoms were observed in the DT group compared with patients in the IT arm. Overall pain-free survival (ie, time to occurrence of asymptomatic progressive disease after IT or DT) was not significantly different (P = 0.79) between arms. The median time to disease progression for patients on the DT arm was 2.8 years less than for IT patients. Cancer-specific survival tended to be longer in the IT group (P = 0.09), but there was no difference in overall survival between groups (P = 0.96). Median survival time was 5.2 years for the IT group and 4.4 years for the DT group.

Conclusion. There were no major advantages to IT compared with DT in patients diagnosed with prostate cancer who were not suitable or declined initial local treatment.

Commentary

Prostate cancer is the most common nonskin malignancy among men. Unlike most common solid tumors, prostate cancer in general is a relatively indolent disease, with patients with advanced disease living several years on average. The standard approach for patients with early-stage disease is to treat with curative intent using local therapy (ie, radiotherapy or surgery). For patients with more advanced disease, hormonal therapy (ie, androgen deprivation) is the standard initial approach. Hormonal therapy has proven to delay PSA progression, palliate symptoms, and prolong survival. However, androgen deprivation is not curative and is associated with significant morbidity adversely affecting quality of life. Thus, a continued debate regarding hormonal treatment pertains to timing.

At least 2 randomized trials have compared IT versus DT. In both trials, IT was associated with an improvement in survival compared with DT [1,2]. However, methodologic criticisms of these trials have led many to question the results. In this trial, Studer et al compare IT and DT in a group of elderly men with locally advanced and advanced stages of disease. The authors found no significant differences in overall survival for IT versus DT. As well, IT and DT were associated with similar pain-free survivals and time until symptom progression.

The strengths of this analysis include its randomized prospective design and well-defined endpoints. It is important to note that this trial was stopped prematurely because of a competing large randomized trial, preventing planned full accrual. All patients enrolled to the date of study closure were followed as originally planned. Unfortunately, the patient population was mixed (comprised of both patients

with nonmetastatic or metastatic disease), making any generalized statements for patients as a group difficult. While not statistically significant, IT was associated with a trend towards improved disease-specific survival, raising the question of whether larger patient numbers would have made this statistically significant. A quality of life analysis was not included in this study, which would have been an important measure in comparing these approaches. Finally, these results do not apply to patients who are considered high-risk for recurrence after local treatment with curative intent.

Applications for Clinical Practice

IT has been associated with lower morbidity, delays in disease progression, and improvements in survival compared with DT in patients with prostate cancer; however, DT may still be appropriate for some patients.

–Review by David R. Spigel, MD

References

1. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol 1997;79:235–46
2. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781–8.