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Adjuvant Hormonal Treatment for Prostate Cancer: The Bicalutamide Early Prostate Cancer Program

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Key Words
Prostate cancer · Adjuvant · Hormonal treatment · Bicalutamide · Radical prostatectomy · Radiotherapy · Watchful waiting

Abstract
Adjuvant hormonal therapy has been demonstrated to be able to delay disease progression in nonmetastatic prostate cancer. To date, however, a favorable impact on survival has only been demonstrated in lymph-node-positive disease and in external-beam radiotherapy series with locally advanced and probably mainly micrometastatic tumors. The Bicalutamide Early Prostate Cancer Program is the largest study under way to define the role of adjuvant treatment in early prostate cancer and identify subgroups of patients likely to benefit from immediate hormonal therapy. At the time of the most recently published analysis, the risk of objective clinical progression was significantly reduced in the bicalutamide arm (hazards ratio 0.58, 95% confidence interval 0.51–0.66, $p < 0.0001$). However, further maturation of data is needed to see whether this difference will lead to a survival advantage.

Adjuvant Treatment for Prostate Cancer

If prostate cancer is organ confined, radical prostatectomy achieves disease-specific 10-year survival rates of about 90% [1]. There are, however, subsets of patients with a markedly less favorable outcome. When disease has spread outside the prostate, survival is compromised. In a multicentric study with 298 stage cT3 patients treated by pelvic lymph node dissection with or without subsequent radical prostatectomy, the prostate cancer-specific 10-year survival rate was only 57% [2]. Radiotherapy alone for locally advanced prostate cancer produced unfavorable results as well [3]. Whereas the long-term outcome after radical prostatectomy is excellent in tumors with a Gleason score of 2–6, the disease-specific 15-year survival is clearly compromised when the Gleason score is 7–10 [4]. In the especially problematic subgroup of patients with Gleason score 8–10 disease, disease-specific 15-year survival after radical prostatectomy is less than 50% [4]. Several clinical trials investigated the effect of adjuvant hormonal therapy to improve these results. Generally, to date, a favorable impact of adjuvant hormonal treatment on survival has only been demonstrated in lymph-node-positive disease and in external-

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Table 1. Overview over selected studies on adjuvant hormonal treatment after curative therapy for prostate cancer

Authors	Year	Setting	Inclusion criteria	Hormonal treatment	Progression	Survival
Pilepich et al. [5] Lawton et al. [6]	1997 2001	RT	stage C or D1	LHRH analogues	advantage for adjuvant treatment	advantage for adjuvant treatment in Gleason score 8–10 subgroup
Granfors et al. [7]	1998	RT	T1–4N0–1	orchiectomy	advantage for adjuvant treatment	advantage for adjuvant treatment in N1 subgroup
Arcangeli et al. [8]	1998	RT	confined to the pelvis	multiple regimens	no advantage for adjuvant treatment	disadvantage for adjuvant treatment
Hanks et al. [9]	2000	RT	T2b–T4, PSA < 150 ng/ml	LHRH analogues plus flutamide	advantage for adjuvant treatment	advantage for adjuvant treatment in high risk subsets (cT3–4 or cT2 with Gleason score 8–10, all Gleason score 8–10 cancers)
Bolla et al. [10]	2002	RT	T1–T4N0–x	LHRH analogues	advantage for adjuvant treatment	advantage for adjuvant treatment
Zincke et al. [11]	1992	RPE	pN+	multiple regimens	advantage for adjuvant treatment	advantage for adjuvant treatment in diploid subgroup
Seay et al. [12]	1998	RPE	pN+	orchiectomy or LHRH analogues	advantage for adjuvant treatment	advantage for adjuvant treatment in diploid subgroup after 10 years
Messing et al. [13]	1999	RPE	pN+	orchiectomy or LHRH analogues	advantage for adjuvant treatment	advantage for adjuvant treatment
Prayer-Galetti et al. [14]	2000	RPE	stage C	LHRH analogues	advantage for adjuvant treatment	not available
Zincke et al. [15]	2001	RPE	seminal vesicle involvement	orchiectomy or oral hormones	advantage for adjuvant treatment	advantage for adjuvant treatment
Wirth et al. [16] Wirth et al. [17]	1997 2003	RPE	stage C	flutamide	advantage for adjuvant treatment	no detectable difference

RT = Radiotherapy; RPE = radical prostatectomy.

beam radiotherapy series with locally advanced and probably mainly micrometastatic tumors (table 1). Adjuvant treatment after the resection or destruction of all macroscopic tumor tissue is intended to prevent progression of suspected microscopic residual cancer. During the last decades, new means of hormonal deprivation (LHRH analogues, antiandrogens) have been developed which allow for reversible and time-limited treatment. Since even in incurable locally advanced or metastatic prostate cancer, immediate hormonal treatment offers only a small survival advantage over deferred treatment after 10 years – detectable only in a meta-analysis including more than 2,000 patients [18] – trials investigating the effect of adjuvant treatment in early prostate cancer require very large numbers of patients enrolled and a long follow-up. The optimal duration of adjuvant treatment and the question whether delayed onset of hormonal treatment (controlled by PSA monitoring) may be as effective as immediate treatment in risk patients [19] remain the subject of an ongoing debate.

The Bicalutamide Early Prostate Cancer Program

In early breast cancer, adjuvant treatment with the antioestrogen tamoxifen resulted in a significant survival benefit over local therapy only [20]. Since prostate cancer is also a hormone-sensitive tumor, it has been hypothesized that early antiandrogenic therapy may be beneficial in this tumor entity as well [21, 22]. In the 'Bicalutamide Early Prostate Cancer Program' (for clinical stages T1b-4N0-1M0), the nonsteroidal antiandrogen bicalutamide is being evaluated as primary or adjuvant therapy for early prostate cancer. The program consists of three double-blind, parallel-group trials (one in North America (trial 23, n = 3,292), one in Mexico, South Africa, Australia and Europe (trial 24, n = 3,603), and one in Scandinavia (trial 25, n = 1,218) [22]. In trial 23, all patients underwent radical prostatectomy or radiotherapy prior to study entry. In trials 24 and 25, watchful waiting was possible as a primary management option besides both treatments with cura-

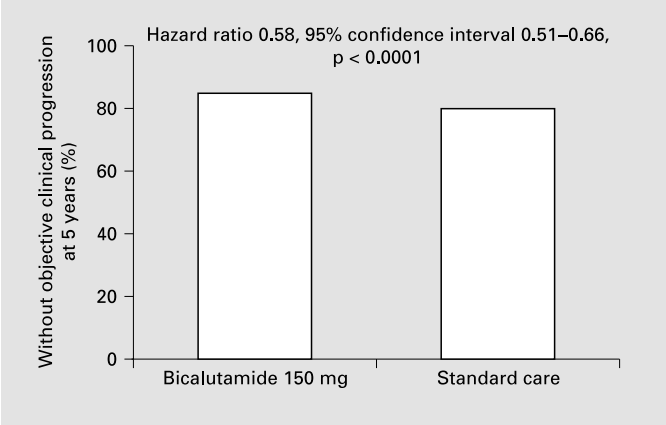

Fig. 1. Freedom from objective clinical progression at 5 years [22].

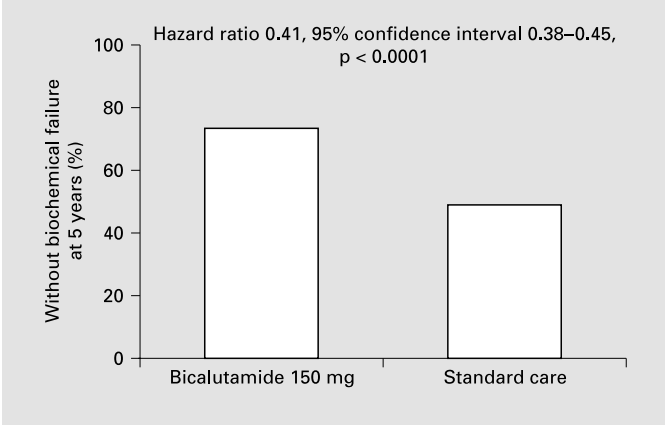

Fig. 2. Freedom from biochemical progression at 5 years [22].

tive intent [21, 22]. For an exact description of the inclusion and exclusion criteria, see See et al. [22]. With a total of 8,113 patients, this program is the largest currently ongoing study on prostate cancer [23]. The patients were randomized on a 1:1 basis to receive either bicalutamide 150 mg once daily (n = 4,052) or placebo (n = 4,061) [22]. In North America, more than 80% had undergone radical prostatectomy and 20% received radiotherapy prior to randomization, compared to 46 and 18% in the Mexico, South Africa, Australia and Europe trial and 13 and 5% in the Scandinavian trial [22]. In North America, more than 70% of patients entered had a tumor stage of less than T3, compared with approximately 60% in Europe and Scandinavia [22–24]. The patients received the adjuvant medication for 2 or more years [22]. Time to objective clinical progression (defined as tumor progression confirmed by either biopsy, bone scan, computerized tomography, ultrasound, or magnetic resonance imaging or death of any causes) and survival are the primary end points in the Bicalutamide Early Prostate Cancer Program [21, 22]. Time to treatment failure (withdrawal from treatment), PSA progression (defined as doubling of the PSA value measured immediately prior to the initiation of the application of the study medication) and tolerability are secondary end points [21, 22]. After a median follow-up of 3 years, 38.1% of patients in the bicalutamide group and 31.8% in the placebo group discontinued the treatment. Adverse events were the most common reason for withdrawal from treatment in the bicalutamide group versus disease progression in the placebo group [22]. Gynecomastia and/or breast pain were the most frequent adverse events in the bicalutamide arm with almost 3 of 4 patients being affected [22]. These symptoms improved or resolved after withdrawal of treatment in the majority of cases. Whereas breast pain disappeared in 84% of affected patients within 1 year after cessation of therapy, the resolution rate of gynecomastia depended on the duration of bicalutamide treatment with only 29% resolution in those patients who took the medication for more than 18 months [22]. At the time of the most recently published analysis [22], 363 patients in the bicalutamide arm and 559 patients in the placebo arm fulfilled the criteria of objective clinical progression (fig. 1). This reduction in the risk of clinical progression by 45% in the bicalutamide arm was highly significant (hazards ratio 0.58, 95% confidence interval 0.51–0.66, $p < 0.0001$). This result needs to be qualified by emphasizing that in trial 23, with its much more favorable risk profile, there was no detectable difference concerning objective progression at this time (83 events in the bicalutamide arm and 87 events in the placebo arm). Overall, the reduction in the risk was observed in the whole study population regardless of the primary (curative or noncurative) treatment. Subgroup analyses revealed a hazards ratio of 0.63 ($p < 0.001$) for patients who had radical prostatectomy or radiotherapy and of 0.53 ($p < 0.001$) for those who did not undergo curative treatment [22]. As expected, the risk reduction was greater in patients with locally advanced disease and in those selected for watchful waiting [22]. Not unexpectedly, considering PSA progression, there was also a highly significant advantage in the bicalutamide arm (fig. 2). For a survival analysis, however, there were too few events observed up to the time of analysis, and a longer follow-up is needed to see whether the delayed clinical progression in the bicalutamide arm will translate into a survival advantage which is the most urgent question to be answered.

Conclusion

Adjuvant treatment for prostate cancer has been shown to provide a survival advantage in patients with histopathologically proven lymph node involvement or with a high risk of microscopic spread. It is, however, still controversial whether a slightly delayed treatment (onset at PSA relapse) may be equally effective. Except for the above-mentioned high-risk patients, randomized trials on adjuvant treatment have so far revealed a delay of progression but no survival advantage in early prostate cancer. The maturation of data of large ongoing trials like the Bicalutamide Early Prostate Cancer Program will increase our knowledge base. However, further studies investigating the appropriate length of adjuvant hormonal therapy are also needed. Efforts are necessary to improve our understanding of factors influencing the survival of men with early prostate cancer.

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