Early versus delayed endocrine therapy for prostate cancer

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Abstract

Endocrine treatment (ET) has in the past been shown to be beneficial in delaying clinical progression in all stages of prostate cancer, leading to an improvement of progression free survival in virtually all trials ever conducted. The first observations on this issue date back to the studies of the Veterans Administration Cooperative Urological Research Group in the 1960s. The period of time during which ET and the resulting side effects can be avoided is strongly dependent on the clinical stage of the disease. This treatment period is long in men who have minimal disease, such as a rising prostate-specific antigen after potentially curative management; however, it is considerably shorter in men who initially present with metastatic disease. In these situations, the potential benefit in quality of life, and avoidance of adverse events must be matched against the benefit in terms of gaining progression free time for the individual patient. This difficult task is supported by information supplied in this review. Locally advanced and regional (lymph node positive; stage T3N0-1MOGx) disease is the domain of adjuvant ET. In this field, important progress has recently been made due to trials, which combine aggressive treatment of the primary tumor with adjuvant ET initiated at the same time. Therefore, in locally advanced and regional disease, radiotherapy or surgery combined with adjuvant ET must be considered state-of-the-art.

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Introduction

Endocrine treatment (ET) of prostate cancer (PC) is more than 60 years old (Huggins & Hodges 1941, Huggins et al. 1941). Huggins and coworkers were awarded the Nobel Prize in 1966 for their studies in endocrine dependence of the prostate, which led to the development of endocrine management for the treatment of PC. ET of advanced PC is recognized as being palliative and is almost invariably used in men with the metastatic condition. The use of early treatment in the course of the disease is discussed in this paper. Important side effects are associated with ET and the desire to reach an optimal balance between adverse events and clinical effectiveness is the main reason for considering delay of ET.

Why delay ET in PC? At the time of diagnosis even advanced PC is often asymptomatic. Patients are therefore confronted with the adverse effects of ET as the only ‘symptom’ of their cancer. Furthermore, depending on the extent of the disease at the time of diagnosis, the natural history may be very long, and avoiding long-term adverse events by delaying ET is desirable. Clearly, there is a need to achieve a balance between the impact of ET on the general well-being and quality of life against the potential clinical benefit.

This review will analyse data from randomized controlled trials of early versus delayed ET (EET versus DET) in various stages of the disease. Some trials utilizing ET in adjuvant settings are included because clinically effective early and delayed ETs are compared.

EET versus DET–evidence of effectiveness

Staging of PC

In this paper, the union international centre le cancer (UICC) classification of PC is used (UICC International Union Against Cancer 1997). In this system, locally confined and locally extensive PC is classified as T1-2 and T3-4 respectively. Regional node positive disease is M1a disease. Metastases to bone are M1b, and other sites are classified as M1c disease.
Endpoints

The main endpoint to be taken into consideration is the overall survival. Cancer-specific survival is of obvious interest because it allows the effect of treatment to be judged in direct relation to the target disease. Intermediate endpoints, such as biochemical progression are relevant mainly in locally extensive disease where the occurrence of bone metastases can be and should be avoided. In this situation, ET can delay metastatic progression (Veterans Administration Cooperative Urological Research Group 1967). The value of endpoints of phase III trials in various clinical situations has been the subject of extensive review (Hall et al. 1997). The specific situation of clinical progression, triggering the initiation of DET in lymph node positive disease is illustrated in Fig. 1, which compares disease free survival with EET and DET in the European Organisation for Research and Treatment of Cancer (EORTC) study 30846 (Schröder et al. 2004a,b). It shows that in men who are managed by DET the time in changing treatment regimen, due to clinical progression under ET, is identical to those who have received immediate treatment. Also, the figure allows estimation of the time course of clinical progression in patients on delayed treatment (median ± 18 months).

Prostate-specific antigen (PSA) is an important biomarker of PC. The possibility that it may be a surrogate for other endpoints, mainly overall survival and cancer-specific survival is intriguing and has recently been investigated (Collette et al. 2003, 2005). The reported results show that outcome predictions strongly depend on the definition of PSA nadirs and reference values during follow-up. Utilizing the meta-analytic approach, it is shown that unfortunately PSA cannot be considered a surrogate for survival at a trial level. PSA remains useful, as an individual predictor of outcome and it may be useful as an intermediate endpoint in phase III studies, allowing a reduction in the duration of such studies in case no effect on PSA is seen. Early marketing of a new drug could be promoted if very large effects on PSA are seen. An advantage in survival would still have to be documented later on.

The issue of EET versus DET needs to take into account the natural history of PC in which early or delayed treatment is considered. While the EORTC study 30846 (Schröder et al. 2004a,b) shows that in lymph node positive disease, without removal of the primary tumor, the median time to progression in the delayed treatment arm amounts to about 18 months. The median time to clinical progression in men with a rising PSA after a radical prostatectomy (RP) has been shown to be in the range of 8 years by Pound et al. (1999). The duration of EET in this setting might amount 13 years or longer. In this situation, considering the quality of life and potential long-term adverse events are particularly difficult because there is a lack of evidence on the effect of treatment and the long-term side effects.

Metastatic prostate cancer

The Medical Research Council (MRC) of the UK conducted a trial of early versus delayed castration, which includes 261 patients with metastatic disease of whom 130 were treated by immediate and 131 by delayed treatment. Results were reported by The Medical Research Council Prostate Cancer Working Party Investigators Group (1997). Initiation of treatment was at the discretion of the participants and timing depended on various types of clinical progression. The study was mature at the time of reporting (recruitment 1985–1993). In the delayed treatment arm, the median time to ET was only 9 months. One hundred and seventy-four out of the 261 men died of PC, 84 (76%) on EET and 90 (80%) on DET. Overall mortality amounted to 224 out of 261, 111 on early and 113 on delayed treatment. There were no significant differences encountered for deaths from any course between immediate and DET (2p = 0.2; NS).

The data of this trial show that there is a very short delay in the treatment of metastatic disease. Out of 131 DET patients, 119 underwent treatment within 9
months of randomization. The present consensus is that cases presenting with metastatic disease should be treated immediately to delay symptoms and to delay further progression. Exceptions are made for men who wish to remain potent, risking the growth of tumours.

Locally advanced and regional disease

Regionally advanced PC with or without positive lymph nodes (T3N0-1M0Gx PC) represents the stage of the disease, in which DET is usually considered. A number of randomized controlled trials are available comparing EET versus DET alone or early ET as an adjuvant to either RP or external beam radiotherapy (EBRT) with either of these treatments as monotherapy in the second arm. ET alone as a third option is presently being explored in the Early Prostate Cancer Program of AstraZeneca and in a Canadian study.

EET versus DET without additional treatment of the primary tumor

The first studies, which in fact addressed the issue of EET versus DET were three separate studies carried out by the Veterans Administration Co-operative Research Group (VACURG 1997) and Byar & Corle (1988). These studies all included arms of various dosages of diethylstilbestrol (DES) and an arm of no treatment. The first study of this series also included castration and castration plus diethylstilbestrol. During the course of a 9-year follow-up period, virtually all men who progressed with metastatic diseases or to metastatic disease in the control arm were eventually treated endocrinologically. It is for this reason that the VACURG studies are considered to be in fact studies of early versus delayed endocrine management. Since there is no difference in overall survival with respect to the original randomization, one important conclusion of the trials was that ET could be delayed without impairing overall survival. The trials however did suggest a positive effect of early treatment on PC related mortality. This effect was exclusively seen in patients who were treated by means of DES in poorly differentiated cancers. The favorable effect of this treatment on PC progression was completely neutralized by an increase in the cardiovascular death rate in the DES arms, which may have been one of the reasons why survival benefit was not shown. Knowledge about these adverse events and their dose dependence is one of the important results of the VACURG studies.

Further to the VACURG studies, there are other randomized trials, which fall into this category. These are EORTC protocol 30846 (Schröder et al. 2004a,b), EORTC 30891, a study which includes locally confined disease and of which the final results have just been reported (Studer et al. 2006), protocol 06-88 of the Swiss Oncology Group (Studer et al. 2004) and the Medical Research Council Prostate Cancer trial in 1997. The results are summarized in Table 1. All trials show at least modest advantages in PC-specific survival for immediate treatment. This translates into an advantage in overall survival only in the MRC trial. However, this favorable difference may be at least partly caused by the fact that 29 out of the 54 cases that died in the delayed treatment arm in excess of the death rate in the immediate arm have never received ET. In the MRC trial, significant differences were seen in favor of early treatment with respect to important disease related complications, such as the rate of spinal cord compression, the rate of urethral

<table>
<thead>
<tr>
<th>Trial</th>
<th>EET, N</th>
<th>DET, N</th>
<th>Median, F.U., years</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirk (1997; MRC)</td>
<td>256</td>
<td>247</td>
<td>&gt;6</td>
<td>(O-E)=20.6, 2p=0.02</td>
</tr>
<tr>
<td>Schröder et al. (2004a;</td>
<td>119</td>
<td>115</td>
<td>8.7</td>
<td>HR=1.23 (NS)</td>
</tr>
<tr>
<td>EORTC 30846)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studer et al., (2004)</td>
<td>100</td>
<td>97</td>
<td>&gt;5</td>
<td>1.6 Years median</td>
</tr>
<tr>
<td>SAKK 08/88</td>
<td></td>
<td></td>
<td></td>
<td>Difference pro EET (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR=0.99 (NS)</td>
</tr>
<tr>
<td>Studer et al., (2006)</td>
<td>493</td>
<td>492</td>
<td>&gt;5</td>
<td>0.8 Years median</td>
</tr>
<tr>
<td>EORTC 30891</td>
<td></td>
<td></td>
<td></td>
<td>Difference pro EET (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR=1.25 (95% CI 1.05–1.48), P=0.06</td>
</tr>
</tbody>
</table>

SACK, Swiss Group for Clinical Research; F.U, Follow-up; HR, hazard ratio; NS, not significant; O-E, observed minus expected.

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obstructions, and the rate of extra skeletal metastases. Most of these problems were not encountered in trials that utilized a more frequent follow-up period, in comparison to the yearly check-ups in the MRC trial.

None of the studies measured quality of life. It can be concluded from the findings of these trials that EET produces a modest improvement in prostate cancer-specific survival and may be related to less serious side effects depending on the type of clinical follow-up employed. No credible and clinically relevant advantage in overall survival was seen.

Protocol EORTC 30846 (Schröder et al. 2004a,b) is of particular importance because it contributes to a better understanding in the role of treatment in the primary tumor in locally advanced and regional disease. In protocol 30846, surgical lymph node dissections were carried out to confirm the N+ status. Subsequently, the prostate was left in situ and randomization was offered to potential participants. The protocol shows a non-significant 23% advantage in the overall survival for the early treatment group. The median time without EET on the DET arm was 18 months. This result is at variance with those trials in which definitive treatment to the primary tumor was applied, specifically (Messing et al. 2006). Data from this latter study are discussed further below.

Studer et al. (2004) reported on SAKK protocol 08/88. One hundred and ninety-seven PC patients with T1-4 N0-2 and M0 (n = 143) or M1 (n = 44) were randomized to immediate or delayed EET (orchidectomy). Follow-up exceeded 5 years, the study was mature, more than 90% of patients were dead at the time of analysis. The study did not reach the projected sample size of 360 patients. There were no significant differences in overall- and PC-specific survival (see Table 1). The median time without EET on the DET arm was 2.8 years. Hemoglobin decreased significantly with EET.

EORTC protocol 30891 was recently closed and the results were published (Studer et al. 2006). Nine hundred and eighty-five men with PC classified as T0-4NO-2M0 randomized to immediate or DET given at the time of clinical progression, the median age was 73 years.

At a median follow-up of 7.8 years, 54.1 out of 985 patients had died, 193 of PC. One hundred and twenty-six patients on the DET arm died without ever requiring treatment, the median time to starting ET in the DET arm was 7 years. The hazard ratio (HR) for overall survival was 1.25 (95% CI 1.05–1.48), testing for non-inferiority showed no significant difference (P > 1). The trend in overall survival was due to fewer non-PC deaths in the EET arm. The authors point out that the long time period of ET and the related side effects, which have been avoided in the DET arm had a median of 7 years (see Table 1).

**EET in lymph node positive PC as adjuvant to RP**

Only one randomized study, ECOG-3886 addresses this issue. Messing et al. (1999, 2006) reported on the ECOG protocol 3886, a study, which was supposed to take on 220 patients but was closed prematurely because of poor recruitment. The most recent report (Messing et al. 2006) included 98 cases; 47 randomized to EET, 51 to DET after pelvic lymph node dissection and a RP. At a median follow-up of 11.9 years in confirmation of the earlier report, significant differences in overall survival (HR = 1.84, 95% CI 1.01–3.05, P = 0.04), PC-specific survival (HR = 4.09, 95% CI 1.96–5.98, P < 0.0001), and clinical progression-free survival (HR = 3.42, 95% CI 1.96–5.98, P < 0.0001) were seen in favor of EET. Differences between EET and DET were significant at P = 0.02 and 0.01, respectively. The study has in the past been heavily criticized because of the small sample size and the fact that an important prognostic factor, the Gleason score, does not correlate with the outcome. In the updated paper (Messing et al. 2006), an independent pathology review is reported. Adjusting for the small differences in Gleason scores at entry did not change the outcome of the survival analysis. In spite of its limitations, the study has determined clinical practice to a large degree.

The interesting question remains: why does this small study show a significant difference, while the much larger EORTC protocol 30846 does not. In Messing and coworkers paper, many urological surgeons around the world left behind the prostate in case of evident lymph node metastases, because the disease was considered to be incurable and it did not seem to justifiable to burden the patients with the side effects inherent to RP. The ECOG study, however, together with the radiotherapy studies, which use ET as an adjuvant have changed the view on the role of the primary tumor in the presence of lymph node metastases. It is likely that, also in view of the results of the radiotherapy trials reviewed in the next section, the interpretation of the results of the ECOG study is correct and that the primary tumor has the capability of contributing to the progression of the disease if it is left behind.

**External beam radiotherapy (EBRT) with and without adjuvant treatment**

Five trials in which interim or end results have been reported, and have compared radiotherapy with adjuvant ET, applied in various settings and at different
durations. A summary of the data together with those of the surgical protocol 30886 are reported in Table 2. Results with a follow-up period exceeding 10 years were reported by Bolla et al. (2002). Four hundred and fifteen cases were treated by radiotherapy applying 70 Gray to the primary tumor and only 50 Gray to the true pelvis. Randomization was between no adjuvant and adjuvant ET for 3 years. Patients were eligible if they had T3 or T4 disease or T1–T2 disease, which was classified as poorly differentiated (G3). ET with the use of luteinizing hormone-releasing hormone (LHRH) agonist was applied for a period of 3 years. Disease free and overall survival was significantly better in the adjuvant ET arm with differences amounting to 15 and 16% at 5 years. Survival data at a follow-up exceeding 10 years were also reported for the Radiation Therapy Oncology Group (RTOG) study 85-31 by Pilepich et al. (2005). Nine hundred and seventy-seven patients with T3 prostate cancer or lymph node positive disease of any T-category were randomized between radiotherapy and radiotherapy plus ET for life. Disease-specific survival is not reported but overall survival at 10 years amounted to 39 vs 24% and 49 vs 39%, respectively, in favor of radiotherapy and adjuvant treatment. This 10% difference is again statistically significant ($P<0.002$). Protocol RTOG 86-10 (Shipley et al. 2002) randomized 456 patients with N+ to N4 disease and large primary tumors that were all estimated to exceed 25 ml in size. The median follow-up was 7.6 years. Radiotherapy to the prostate and the whole pelvis was applied. The trial compared radiotherapy plus 4 months of neo-adjuvant and adjuvant ET during radiotherapy to radiotherapy alone. Adjuvant treatment was associated with an advantage of 3% in disease free and no difference in disease free and overall survival. The ET periods were likely to be too short. A significant difference was however seen for tumors classified as Gleason 2–6.

RTOG trial 92-02 (Hanks et al. 2003) recruited 1554 patients classified as T2c-T4 with PSA values at diagnosis not exceeding 150 ng/ml. The median follow-up was 4.8 years. Randomization was between radiotherapy, again applied to the prostate and to the whole pelvis, plus 24 months of ET against radiotherapy, plus 2 months of neo-adjuvant and 2 months of adjuvant treatment. Disease-specific survival showed a significant advantage of 16% for the 24 months ET arm ($P=0.001$) and no advantage in overall survival. If the participants were retrospectively classified according to the entry criteria of EORTC 22863 and the presence of Gleason scores 8–10, overall survival amounted to 80 vs 69% in favor of the 24 months ET ($P=0.007$). The trial reported by D’Amico et al. (2004), selected locally confined cases with Gleason scores of 7 or higher. Two hundred and six patients were recruited; the median follow-up amounted to 4.5 years. Radiotherapy was limited to the prostate and given at a dosage of 70 Gray. ET of 6 months duration was initiated at the time of radiotherapy in one out of the two arms. In the combination arm, no single patient died of prostate cancer, while six PC deaths occurred in the radiotherapy only arm. Overall survival differed significantly ($P=0.04$) by 10% in favor of the adjuvant ET arm. In all trials reported, patients who progressed on the radiotherapy only arm were subsequently treated by endocrino- logical means.

The most important observation to be derived from the data reported in this section is the significant improvement of cancer specific and overall survival in most of the mature trials utilizing adjuvant ET for prolonged periods (>4 months) with aggressive treatment of the primary tumor either by surgery or by radiotherapy. The variable schemes of adjuvant ET reflect uncertainty at the time when these trials were initiated. It is remarkable that the study by D’Amico

### Table 2 Randomized trials of early versus delayed endocrine treatment (EET versus DET) as adjuvant with surgery or radiotherapy in loco-regional prostate cancer (PC)

<table>
<thead>
<tr>
<th>Study</th>
<th>EET, N</th>
<th>DET, N</th>
<th>F.U., years</th>
<th>Survival</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 3886 Messing et al. (1999)</td>
<td>47</td>
<td>51</td>
<td>7.1</td>
<td>94 vs 69%</td>
<td>85 vs 65%</td>
</tr>
<tr>
<td>EORTC 22836 Bolla et al. (2002)</td>
<td>207</td>
<td>208</td>
<td>&gt;10</td>
<td>94 vs 79%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78 vs 62%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>RTOG 85-31 Pilepich et al. (2005)</td>
<td>488</td>
<td>489</td>
<td>7.6</td>
<td>39 vs 24%</td>
<td>49 vs 39%</td>
</tr>
<tr>
<td>RTOG 86-10&lt;sup&gt;b&lt;/sup&gt; Shipley et al. (2002)</td>
<td>227</td>
<td>229</td>
<td>9.0</td>
<td>50 vs 50%</td>
<td>41 vs 44%</td>
</tr>
<tr>
<td>RTOG 92-02 Hanks and Polak (2003)</td>
<td>1554</td>
<td>4.8</td>
<td>89 vs 83%</td>
<td>80 vs 87.5% (NS)</td>
<td>0.001</td>
</tr>
<tr>
<td>D’Amico et al. (2004)</td>
<td>102</td>
<td>104</td>
<td>4.5</td>
<td>6 vs 0%</td>
<td>88 vs 78%</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; F.U., follow-up; NS, not significant.

<sup>a</sup>5-Year survival.

<sup>b</sup>4-Month neo-adjuvant and adjuvant MAB during RT.
et al. (2004), which selected for locally confined poorly differentiated cases and utilized only 6 months of ET started at the time of radiotherapy, revealed a significant survival advantage already after 4.5 years. This means that prolonged periods of ET utilized in some of the other studies may be unnecessary. The trials also leave uncertainty with respect to the usefulness and need of neo-adjuvant ET. As a result of the data presented, standard treatment of locally extensive PC with or without lymph node metastases (T3-4N0-1M0Gx) is radiotherapy combined with adjuvant treatment for a period of at least 6 months with or without a preceding period of neo-adjuvant ET, which will at least have the advantage of producing a smaller prostatic volume to be irradiated. Also, in most centers, the data of ECOG 3886 have led to a change of policy and removal of the primary tumor and initiation of ET at the time of the diagnosis of lymph node metastases instead of abandoning RP in this situation.

Meta-analysis

A meta-analysis going back to the original data of all trials in the field is in preparation by the Prostate Cancer Trialists Co-operative Group. Preliminary results have been presented at the meeting of the Federation of European Cancer Societies ECCO12 in Copenhagen in 2004 by Peto & Dalelio (2004). An overview over the results including most of the data of the preliminary version of the meta-analysis is available through the website of the federation meeting ECCO12 in Copenhagen 2004. The meta-analysis includes data of 3372 men randomized between EET and DET who at the time of the analysis had a follow-up of at least 10 years. The study group is waiting for the data of EORTC protocol 30891 to become available for inclusion (Studer et al. 2004).

The preliminary data show a difference of 11.5% at 10 years in PC-specific mortality, which translates into a difference of 7.2% in overall mortality in favor of early orchidectomy or LHRH agonist treatment. Contrary to the studies utilizing DES, there is no difference in non-prostate cancer mortality in studies using castration or an LHRH analogue. Much of the significant differences in PC-specific and overall mortality seen in this meta-analysis is due to the trials which combine surgery or radiotherapy with adjuvant ET (ECOG 3886, EORTC 22863, and the RTOG trials referred above). Adjuvant ET to surgery or radiotherapy of the primary tumor will be considered separately from pure EET versus DET trials.

Adjuvant treatment in locally confined disease

The early PC program of AstraZeneca has included 8113 patients into three similar trials run in the US (See et al. 2003), Scandinavia (Iversen et al. 2004), and in the rest of Europe (Wirth et al. 2004). The North-American trial has included 3392 men, the Scandinavian trial 1218, and in the European trial 3603 men. Randomization was between 150 mg casodex versus placebo. The endpoints are disease progression and survival. There were slight differences between the US and the European trials. All included the adjuvant setting for patients undergoing RP or radiotherapy. The European trials in addition allowed patients selected for watchful waiting. The US trial excluded, the European trial included N+ disease. The period of therapy in the US trial was 2 years. In the European trials, therapy was planned for a period of 5 years or until clinical progression. Data from the third analysis carried out in 2005 have been published with a median follow-up of 7.4 years over all three studies. Patients with ‘locally advanced’ disease showed a significant advantage in progression free survival in the overall analysis (HR=65, P=0.03). However, in ‘localized’ disease, there was a trend toward a decreased overall survival (HR = 16, P=0.07). No differences were seen in the RP subgroup (McLeod et al. 2006).

A pre-planned exploratory analysis, according to a prognostic sub-classification of the cancers at the time of diagnosis was carried out in 2003 between the categories watchful waiting and adjuvant localized, and watchful waiting and adjuvant advanced. This analysis showed inferiority of castration to placebo in the patients classified as localized (HR=1.47) and superiority of bicalutamide in those classified as advanced (HR=0.68; Iversen et al. 2004). It was subsequently recommended that remaining patients on active treatment in the localized group should discontinue casodex, while all patients in the locally advanced group were offered casodex treatment. An analysis of the causes of death in the subgroups of the exploratory analysis did not reveal any differences that would point in the direction of an adverse effect related to casodex treatment. All three studies show that very long-term observations are necessary to evaluate the effect of ET in men with localized disease. This is in line with the observations of Pound et al. (1999).

Adverse effects of ET

Most adverse events of currently used types of endocrine management of PC can be directly related.
to underlying endocrinological mechanisms. The specific side effects of monotherapy with anti-androgens will only for some part be discussed in the context of this review. The specific adverse events seen with flutamide and cyproterone acetate were subject to comparison in a randomized study of the EORTC-GU group (protocol 30892). Painful gynecomastia, nausea and diarrhea were more frequently seen with flutamide and occurred at rates of 43, 17, and 23%, respectively and cardiovascular problems were equally distributed between arms. Flutamide toxicity required discontinuation of treatment in 17.9% as opposed to 7.2% with cyproterone acetate (Schröder et al. 2004a,b).

LHRH agonists are used in subcutaneously injectable preparations and leads after an initial rise of gonadotropins, to a decrease in LHRH and testosterone. In cases with metastatic disease, especially in symptomatic patients, the initial rise of plasma testosterone can lead to an increase of clinical symptoms and even death (the flare phenomenon) which is usually prevented by an anti-androgen at least during the initial treatment period (Thompson et al. 1990). Continuous treatment by combining an LHRH agonist and an anti-androgen (total androgen blockade or maximal androgen blockade) is not discussed in this review, which will be limited to the side effects of castration and LHRH monotherapy, the treatment principles most frequently used in early versus delayed regimens. The primary goal of endocrine therapy is to reach castrate levels of plasma testosterone. Castrate levels of plasma testosterone have in the past been defined as ranging from 0.7 to 1.7 nmol/l (20–50 ng/100 ml), but have more recently been redefined as < 0.7 nmol/l (<20 ng/100 ml; Oeffelein et al. 2000). Tissue androgen levels were subject to much debate; testosterone is the substrate of 5-α-reductases type I and type II. Type II is predominantly located in the prostate and produces 5-α-dihydrotestosterone (DHT), the most active androgen in prostatic development and function. Remaining DHT levels derived from adrenal androgens can be blocked by anti-androgens. This has resulted in the concept of maximal androgen blockade (Labrie et al. 1988). Unfortunately, initial expectations related to this concept were not confirmed by evidence from randomized studies and in a recent meta-analysis (Prostate Cancer Trialists’ Group 2000). The most definitive single randomized study is South West Oncology Group (SWOG) Intergroup protocol 105 of which Eisenberger et al. (1998) reported negative results. Maximal androgen blockade has been rarely used in EET versus DET trials. The differential side effects of this regimen will therefore not be addressed.

### Adverse events

Adverse events of ET are related to the sudden and drastic decrease of the production of testosterone and the decreasing plasma testosterone levels. Since castration and LHRH agonists are almost exclusively used in metastatic or regionally extensive PC and survival of patients with such conditions is limited, virtually no knowledge is available concerning side effects occurring with ET of a very long duration, therefore, ET is necessary in men with locally confined disease or a rising PSA after potentially curative management.

### Libido and sexual function

Libido and sexual potency rapidly decreases after castration in line with the occurrence of hypogonadic testosterone levels. It is unexplained why even with long-term observations, more than 20% of castrated men remain sexually active and claim normal erectile function (Ellis & Grayhack 1963). With the use of anti-androgen monotherapy, sexual function decreases more slowly (by about 50% per year), but eventually reaches a 20% level (Schröder et al. 2000). This very slow decrease of sexual functioning has led authors of studies with short-term observations to overestimate the rates of libido and continuing erectile function with this form of treatment.

### Hot flushes

Hot flushes are the most frequent adverse effect of castration and LHRH management occurring in almost 80% of patients (Holzbeierlein et al. 2004). More than a quarter of these men experience hot flushes as the most bothersome adverse event. Hot flushes can occur many times per day and can lead to the necessity to take frequent showers and change clothing several times per day. Radlmaier et al. (1989) have elucidated the endocrine mechanism and showed that cyproterone acetate, which is available in Europe but not in the US is an effective treatment. Megestrol acetate, a progestagen with some androgenic activity, has been studied and shown to significantly decrease the frequency of hot flushes (Loprinzi et al. 1994). However, a study by Dawson & McLeod (1995) showed a rise of PSA with megestrol acetate treatment. The PSA decreased again with discontinuation. So, unquestionably, the androgenic properties of megestrol acetate may lead to a stimulation of PC. This treatment is therefore not applicable to this group of men.
Changes of bone mineral density and fractures

Daniell (1997) have compared the risk of spontaneous fractures in castrated and normal men over a period of 9 years. After this time period, the risk of fractures was 50% in the castrated and 7% in the non-castrated group. Several recent studies have shown that bone mineral density (BMD) decreases significantly after castration. This decrease goes beyond the change of BMD in post-menopausal women as shown by Shahinian et al. (2005). However, the same study shows that at 5 years of observation the rate of spontaneous fractures is 19.6 and 12.4% in men with and without androgen deprivation. Skeletal complications increase with the duration of the castrate condition in all reported studies. A recent randomized study has revealed that zoledronic acid given at a dosage of 4 mg every 3 months for a period of a year significantly decreased the loss of BMD and symptomatic skeletal adverse events. Pre-existing osteoporosis is a significant risk factor. These men are probably the best candidates for additional treatment with bisphosphonates after castration or with the use of LHRH agonist depots (Saad et al. 2002).

Metabolic and cognitive changes

Serum testosterone levels are positively related to muscle mass and correlate negatively with the body mass index (BMI). The changes include the increase in the total fat mass of the body. A recent review of these changes is available by Smith (2003). A recent report by Yannucci et al. (2005) suggests changes in cholesterol and blood lipid composition with an increase of HbA1c. Keating et al. (2006) studied a cohort of 73 196 Medicare insured men with PC. They found that with the use of GnRH agonists, the adjusted HRs for diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death were modestly but significantly increased with respect to HR of 1.44, 1.16, 1.11, and 1.16. After castration, the risk of developing diabetes was only increased (HR = 1.34).

While at this moment, there is no evidence that these metabolic changes increase the risk of cardiovascular events, their long-term persistence with long-term endocrine management in M0 disease might still lead to cardiovascular complications. In this author’s view, especially men with cardiovascular risk factors should be monitored carefully. Cognitive and mood changes have been described among others by Green et al. (2002, 2004). A recent prospective study describes declines in visual memory, visual recognition, and verbal fluency with castration (Salminen et al. 2005). Herr & O'Sullivan (2000) studied quality of life in 145 men given a choice of immediate or deferred castration. Those choosing immediate treatment fared significantly worse with respect to fatigue and factors of psychological distress. Fatigue has been related to anemia by Strum et al. (1997), other authors found an eight times increased rate of depression with respect to US national averages (Pirl et al. 2002).

Adverse events of androgen withdrawal by either castration or the use of LHRH analogues are significant and relevant to patients. While short-term adverse events are well understood, studies covering long periods of time are rare and limited to protocol 30891 of the EORTC (Studer et al. 2004). This is a factor that needs to be taken into account when immediate versus delayed endocrine management is considered in men who are known to have conditions, with a very long natural history, such as locally confined PC or a rising PSA after RP or radiotherapy. Considering the potential side effects of ET, obviously has to be individualized when a decision about immediate or delayed treatment is to be taken. Clearly, in a person who is no longer sexually active, or who may present with erectile dysfunction from the start; the decision elements are different from a man who wishes to continue to enjoy a sexual life. Also, the decision on early versus delayed treatment should be influenced by tumor stage and risk factors for important adverse effects, such as pre-existing osteoporosis or cardiovascular disease, which may be sensitive to an adverse change in BMI. Overall, the gain in quality of life during the estimated period of time, during which a given patient can remain free of ET requires consideration of the potential adverse events, briefly summarized above against potential risks of delaying ET specifically if it can be combined with radiotherapy.

Conclusions

The available information on early versus delayed treatment applied in randomized controlled trials of PC shows modest advantages of early treatment. These are strongly dependent on the stage of the disease. In metastatic disease, the window for delaying ET is extremely short, the survival advantages of delaying ET could not be shown. Therefore, the consensus is that cases of metastatic disease should be treated by endocrine means to offer the benefit of delay or further progression and temporary suppression of symptoms. In loco-regional disease (T3-4N0-1M0Gx), most trials show an advantage in PC-specific mortality, which in some trials translates into a significant advantage in overall survival. Most studies, combining either
surgery or radiotherapy with adjuvant ET, show significant and clinically relevant advantages for adjuvant early ET in cancer specific and overall survival. This advantage was not seen in an EORTC study of men with node positive disease in which the primary tumor was left in place. These trials have changed clinical practice in loco-regional disease toward aggressive treatment of the primary tumor and adjuvant ET. But the best regimen and duration of ET is still a subject of discussion.

Two adjuvant studies of early treatment in locally confined PC conducted within the early PC program of AstraZeneca, show advantages in progression-free survival, but with a follow-up of 5.4 years in 2003, this study is immature with respect to survival except in the high risk group in the Scandinavian part of the program. The studies confirm the very low rate and the long time course to disease progression after failure of potentially curative management of locally confined disease.

In locally confined PC in the more advanced stages, it is necessary to balance the potential adverse effects against the so far minimal advantages of EET.

Side effects of ET are extensively described and referenced. They strongly depend on the duration of treatment. Obviously, loss of sexual functions will be experienced less severely in men who are sexually inactive at diagnosis. In applying EET versus DET, the potential benefit must be balanced against the impact of the adverse effects of endocrine therapy.

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