A Multidisciplinary Team Approach for the Optimal Clinical Management of Metastatic Hormone-Refractory Prostate Cancer—Case Study

John Fitzpatrick *

Mater Misericordiae Hospital, University College Dublin, 47 Eccles Street, Dublin 7, Ireland

Panel: John Anderson, Ronald de Wit, Mario Eisenberger

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Abstract

Patients with prostate cancer often require a multimodal treatment approach and the expertise of a multidisciplinary team for optimal management. This is illustrated by the case study of a 59-yr-old man with a prostate-specific antigen (PSA) level of 11.4 ng/ml, who was otherwise fit and well. He had negative bone scans and transrectal ultrasound-guided biopsies revealed a Gleason score of 8 (4 + 4). The panel identified the patient as having seemingly localised prostate cancer with a high risk of PSA recurrence at 5 yr. Although a potential candidate for radical prostatectomy, the panel recommended that the patient should be informed of the risk of lymph node involvement and exploratory surgery performed. Metastatic disease was detected on lymph node frozen section. Accordingly, the patient did not undergo prostatectomy and received a luteinising hormone-releasing hormone agonist instead. After an initial response, the patient’s PSA slowly slipped upwards again, and he then received complete androgen blockade, despite evidence suggesting that the benefit of this approach is minimal. A bone scan and a magnetic resonance imaging scan both revealed metastatic disease, although the patient remained asymptomatic. Data from the TAX 327 study support the use of chemotherapy in asymptomatic patients with metastatic hormone-refractory prostate cancer and therefore docetaxel every 3 wk represents a viable treatment option for this patient. The maintenance of close working relationships between urologists and oncologists will produce a multidisciplinary approach that promises, through the timely use of chemotherapy, to provide patients with the best chance of survival and quality of life.

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* Tel. +35 31 83 08 530; Fax: +35 31 83 08 530.
E-mail address: jfitzpatrick@mater.ie.
1. **Introduction**

Patients with prostate cancer often require a multimodal treatment approach and therefore the expertise of a multidisciplinary team for optimal management. There has been a long-standing reluctance on the part of urologists to refer patients with advanced disease to the medical oncology team. However, data from the TAX 327 and SWOG-99-16 studies highlight the need for an integrated, multidisciplinary approach, in which urologists and oncologists use their combined clinical judgement to implement the timely use of chemotherapy.

2. **Patient history**

A 59-yr-old man presented in October 2002. He had experienced erectile dysfunction for 12 mo and had accompanying mild lower urinary tract symptoms. His prostate-specific antigen (PSA) was 11.4 ng/ml and he had a history of hypertension, but was otherwise fit and well.

3. **Investigative studies**

On rectal examination, he had a firm nodule within the left lobe of his prostate. Transrectal ultrasound-guided (TRUS) biopsies revealed a Gleason score of 8 (4 + 4) in three of five biopsies taken from the left side (i.e., clinical T2a prostate cancer). The patient was very keen for active treatment and had negative bone scans. What are the treatment options for this man?

**ANDERSON:** I am concerned about this man. He has high-risk, seemingly localised prostate cancer and the probability of PSA recurrence at 5 yr is >50%. He also has a <20% chance of organ-confined disease and the chance of lymph node involvement stands at about 20%. There is, therefore, a strong rationale for the use of active treatment in this man, especially because the patient himself is pushing for a proactive treatment strategy; this is not a case in which you would merely observe the patient over time. Surgery and radiotherapy are two possible active treatments for this patient; however, neither of these in isolation is likely to be curative. This man is therefore the perfect example of a patient in whom a multimodal treatment approach is required. The combination of surgical intervention (i.e., radical prostatectomy) and adjuvant hormonal therapy or adjuvant radiotherapy will give this patient the best chances of disease control.

**EISENBERGER:** The probability that this patient, with a Gleason score of 8, has organ-confined disease is, according to the Partin tables, very low. Furthermore, even if this patient had organ-confined disease, the probability of biochemical recurrence within 5 yr is still very high. Treatment of this patient is therefore a matter of choice, but we must acknowledge the fact that, in both cases, the patient is at high risk of disease recurrence. We have seen that there are a number of ongoing clinical studies involving patients with localised disease who are at high risk of disease progression, and enrolment into these clinical trials should be considered.

Cooperative group trials evaluating the multidisciplinary management of men with early-stage prostate cancer are often hindered by slow accrual. There is the need for improved communication between medical oncologists, urologists, and radiation oncologists, as well as the involvement of all disciplines in the planning and design of, and recruitment for, phase 3 studies that will define the role of different treatment strategies in the care and management of high-risk patients with localised disease.

The consensus treatment approach for this patient is radical prostatectomy, assuming that the histological evidence supports such intervention.

4. **Patient undergoes explorative surgery**

The patient had a pelvic exploration with a view to radical prostatectomy and the lymph nodes were found to be enlarged bilaterally. The lymph nodes were then sent for frozen section.

**ANDERSON:** The patient should be informed in advance that the chance of lymph involvement, according to the Partin tables, is about 20%, and that if the presence of positive lymph nodes is confirmed through frozen section, radical prostatectomy may not be the best course of action. It is therefore important to wait for the results of the frozen section before proceeding with treatment.

Lymph node frozen section revealed metastatic disease in the left prostate and reactive lymph nodes in the right prostate. These observations were confirmed by paraffin sections that revealed metastatic adenocarcinoma in the lymph nodes with extension into adjacent adipose tissue—pT2a, pN1, MX.

Would the observation of lymph node-positive disease influence your decision to perform a radical prostatectomy?

**ANDERSON:** Indeed. Some patients, despite being informed in advance that the presence of positive lymph nodes reduces the viability of radical prostatectomy, are still keen to proceed with surgery.
There is no evidence, however, of any benefit to patients of such an approach. Accordingly, the patient did not undergo prostatectomy. Instead, in November 2002, he was started on a luteinising hormone-releasing hormone (LHRH) agonist. This approach is supported by the findings of the Eastern Cooperative Oncology Group (ECOG) study, performed under the leadership of Edward Messing, which randomised 98 men with prostate cancer that had spread to pelvic lymph nodes at the time of surgery. These men received immediate antiandrogen therapy (with either goserelin, an LHRH agonist, or orchietomy) or were followed until disease progression. There was a dramatic increase in survival for patients treated with early androgen withdrawal [1]. This study has been criticised by some, especially researchers at Johns Hopkins in the United States, including Mario Eisenberger [2].

EISENBERGER: The ECOG study was a small study and therefore represents only a small subset of patients. Our concerns focus on the extrapolation of the findings of this small study to a much larger population of patients with prostate cancer. The conditions of the study also fail to reflect current clinical practice because patients were randomised to either immediate hormonal therapy or deferred hormonal therapy on disease progression to bone metastases. Nowadays, >70% of patients will receive hormonal therapy before the appearance of bone metastases.

The patient’s PSA response to LHRH therapy is summarised in Table 1. After 6 mo of treatment, the patient’s PSA dropped to 0.2 ng/ml; however, it was then observed to slowly slip upwards again, reaching 4.0 ng/ml in August 2004. At this time, the patient received complete androgen blockade. The addition of an antiandrogen at this stage is a common occurrence in clinical practice. What is the rationale for such an approach?

DE WIT: If there are castration levels of androgen, the impact of adding an antiandrogen to LHRH agonist blockade is minimal. However, patients are crucially aware of their rising PSA levels and therefore the threshold for adding an antiandrogen in clinical practice can be very low.

EISENBERGER: Following androgen ablation, there are many changes to the androgen receptor, including an amplification of the androgen receptor gene that increases its sensitivity to steroid hormones and eventually leads to the development of hormone resistance. However, the addition of an antiandrogen to initial hormonal strategies is the standard of care for patients with prostate cancer despite being associated with side effects, most notably gynaecomastia and abnormal liver function. Not all patients would be expected to respond to an antiandrogen and therefore such use should be restricted to patients in whom there is evidence of rising PSA despite hormonal ablation.

5. Imaging studies

The patient had a bone scan that revealed a solitary area of intensely raised uptake in the sacrum (Fig. 1). Furthermore, a magnetic resonance imaging (MRI) scan showed a low signal on T1-weighted and T2-weighted images in the second and third sacral segments. These findings are consistent with bone metastases (Fig. 2).

The patient remained asymptomatic; no pain or other problems were reported. His quality of life (QoL) remained good and he was able to continue sailing.
with his family and golfing with his friends every weekend. Therefore, his treatment was not changed. In January 2005, the patient’s PSA level reached 8 ng/ml, but he remained asymptomatic. What are your guidelines for treatment for this patient, specifically the use of docetaxel-based chemotherapy?

DE WIT: If one focuses on the data obtained from the TAX 327 study, patients with metastatic hormone-refractory prostate cancer (mHRPC) who were symptomatic had similar benefits to those who were asymptomatic. The obvious question that arises from this observation is whether chemotherapy, with its associated side effects, should be initiated in an asymptomatic patient. To answer this question, it is important to emphasise that there are different ways to elicit an improvement in a patient’s QoL. If a patient is symptomatic, his QoL can be significantly improved by the relief of pain. Similarly, if a patient can restart his usual activities of daily living, such as washing the car or gardening, the benefits of treatment are again clearly measurable. If a patient is asymptomatic, and therefore treatment is sought owing to rising PSA levels, the use of chemotherapy is still justified, because patients are aware that an increasing PSA level is associated with decreased survival and that, therefore, any strategy capable of lowering the PSA will improve their overall survival. These patients will often experience an improvement in QoL as soon as they become aware that the PSA is decreasing. The decision about when to initiate chemotherapy must therefore be made on an individual basis and should not be unnecessarily delayed.

6. Conclusions

mHRPC is no longer considered to be a chemoresistant disease. Docetaxel 75 mg/m² every 3 wk (q3w) has emerged as the new standard of care for these patients, offering survival benefits without compromising QoL. Urologists and oncologists are therefore faced with the challenge of determining when to best use chemotherapy in patients with prostate cancer, thereby optimising the treatment strategy for these patients. The importance of close working relationships between urologists and oncologists is evident from the above case study. On diagnosis, the patient was identified as a potential candidate for radical prostatectomy; however, investigative studies revealed lymph node involvement and metastatic disease indicating a systemic approach was necessary. Although the initial response to hormonal therapy was promising, the patient soon progressed to mHRPC despite remaining asymptomatic. Data from the TAX 327 study support the use of chemotherapy in asymptomatic patients with mHRPC and therefore docetaxel q3w represents a viable treatment option for this patient. This multidisciplinary approach promises, through the timely use of chemotherapy, to provide patients with the best chance of survival and QoL.

Conflict of interest

This article was developed from a presentation given at a scientific symposium sponsored by sanofi-aventis at the European Association of Urology (EAU) Annual Congress, Paris, France, 5–8 April 2006.

References