DOCETAXEL FOR THE TREATMENT OF HORMONE REFRACTORY METASTATIC PROSTATE CANCER

A Submission of Evidence to the NICE Health Technology Appraisal Committee on Behalf of the Royal College of Physicians, the Association of Cancer Physicians, the Royal College of Radiologists and the Joint Collegiate Council for Oncology

Introduction

Prostate cancer is the commonest male cancer in the UK. There is a 1 in 13 lifetime risk of being diagnosed with prostate cancer. Age specific incidence rates have increased in all age groups over the age of 45 in the last 15 years.

In 2002 9,937 men died of prostate cancer (the second biggest cause of cancer death after lung cancer) which represents a death rate of 34.6 per 100,000 population.

Current Management of Metastatic Prostate Cancer

Over 80% of men who develop metastatic prostate cancer have an objective response (measured by PSA reduction) and improvement in symptoms after receiving androgen ablation therapy usually by medical or surgical castration. This response lasts a median of 18-24 months.

Patients who develop androgen independent (refractory) metastatic prostate cancer have a median survival of 10-12 months. Further response rates of up to 30% are seen with second line hormonal manipulation, e.g., oestrogens, pure anti-androgens and ketoconazole.

The use of chemotherapy in androgen independent prostate cancer was investigated by Tannock et al, Berry et al and Kantoff et al in the 1990s. The studies showed that mitozantrone plus a cortico-steroid improved symptoms and quality of life in men with metastatic prostate cancer but there was no improvement in survival noted. In view of the improvement in palliation mitozantrone plus a cortico-steroid has become the standard chemotherapy regimen for metastatic prostate cancer in North America and the UK.

Docetaxel

Docetaxel is a taxane drug which is active in a variety of solid tumours e.g., breast and lung cancer. It disrupts the microtubular network which is essential for mitotic and interface cellular functions; it also phosphorylates BCL-2 in vitro, leading to its inactivation and eventual cell death by apoptosis.

Seventeen open label phase II studies have investigated the use of docetaxel with or without estramustine in androgen independent prostate cancer. Docetaxel was given weekly or three-weekly. Response, defined by a decrease of PSA level by greater than 50% from baseline was seen in between 34 and 80% of patients treated with single agent docetaxel. In studies where docetaxel was combined with estramustine response rates were between 45 and 86%. These

encouraging results led to phase III studies which were published in October 2004 (Petrylak et al and Tannock et al).

Phase III Studies of Docetaxel in Metastatic Prostate Cancer

In the North American study published by Petrylak et al, 770 men were randomised to receive either docetaxel (60 mg/m^2) with dexamethasone and estramustine or alternatively to receive mitozantrone 12 mg/m^2 plus prednisolone 10 mg daily. The results of the study showed an improvement in median survival from 15.6 months in the mitozantrone arm to 17.5 months in the docetaxel arm. This difference was statistically significant with a hazard ratio for death of 0.8 (confidence interval 0.67-0.97). Fifty percent of patients in the docetaxel group had an objective PSA response compared to 27% in the mitozantrone group.

Adverse events were seen more commonly in the docetaxel plus estramustine arm of the trial. Adverse events lead to the withdrawal of 16% of the docetaxel arm and 10% of the mitozantrone arm of the trial; there were eight deaths in the docetaxel arm compared to four in the mitozantrone arm; there were significantly higher rates of grade III or IV neutropenic fevers (5% versus 2%), cardiovascular events (15% versus 7%), nausea and vomiting (20% versus 5%), metabolic disturbances (6% versus 1%) and neurological events (7% versus 2%) in the docetaxel plus estramustine arm.

Tannock et al in an international three armed study of 1,006 men compared a control arm of mitozantrone (12 mg/m^2) and prednisolone (10 mg daily) repeated every three weeks with 2 docetaxel containing arms: all patients received prednisolone as in the control arm with either docetaxel 75 mg per m^2 every three weeks, or docetaxel 30 mg/m^2 weekly for five out of six weeks. Patients in the three-weekly docetaxel arm had a significant improvement in median survival to 18.9 months from 16.5 months in the mitozantrone arm (hazard ratio 0.76 - confidence intervals 0.62-0.94). Patients in the weekly docetaxel arm had a median survival of 17.4 months which was again significantly better than in the mitozantrone control arm (hazard ratio 0.91 - confidence intervals 0.75-1.11). PSA response greater than 50% was seen in 32% of mitozantrone group, 45% in the docetaxel three-weekly and 48% in the docetaxel weekly treatment arms.

There was a higher rate of grade 3 and 4 neutropenia with three-weekly docetaxel (32%) versus mitozantrone (22%). Grade 3 and 4 neutropenia occurred in 2% of the docetaxel weekly group. There was increased incidence of cardiac toxicity as measured by left ventricular ejection fraction in the mitozantrone group (22%) compared to docetaxel three-weekly (10%) and docetaxel weekly (8%). The symptoms of fatigue, alopecia, diarrhoea, nail changes; sensory neuropathy, stomatitis and peripheral oedema were seen more commonly in the docetaxel groups as compared to the mitozantrone arm. At least one serious adverse event occurred in 26% of docetaxel three-weekly, 29% of the docetaxel weekly and 20% of the mitozantrone groups. Treatment related death occurred in three patients in the mitozantrone group and one patient in each of the docetaxel groups.

Quality of life using FACT-P was evaluated in 815 patients. Improvement in quality of life was seen in 22% of the docetaxel three-weekly and in 23% the docetaxel weekly compared to 13% in the mitozantrone group.

In both studies the median age of patients was between 68 and 70. More than 85% of patients had a good performance status prior to treatment. In the Tannock study greater than 90% of patients had at least two hormonal manipulations prior to entry into the study.

Summary

Both phase III studies have, for the first time in patients with androgen independent metastatic prostate cancer, produced a statistically significant prolongation of survival when compared with the former standard treatment of mitozantrone and a corticosteroid.

The Tannock study has shown evidence of improvement in quality of life despite there being an increased incidence of adverse events in patients treated with docetaxel.

Indirect comparisons across the 2 trials would suggest that the combination of docetaxel and estramustine is more toxic than docetaxel plus prednisolone.

Conclusion

It is concluded from the published evidence that docetaxel 75 mg per m^2 every three weeks plus prednisolone 10 mg daily should now be adopted as the chemotherapy regimen of choice in patients of good performance status with androgen independent (hormone refractory) metastatic prostate cancer in the UK.

The optimal timing of use of docetaxel plus prednisolone with respect to the course of disease is not certain and this may require further investigation. On the basis of this study it could be considered after disease progression following at least two hormone manipulations and provided performance status remains good (WHO performance status 0-1 or Karnofsky of greater than 60%).

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March 2005