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Clinical Oncology Update: Prostate Cancer

The Assessment of Treatment Outcomes in Metastatic Prostate Cancer: Changing Endpoints*

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INTRODUCTION

THE MODERN era of clinical trials in metastatic prostate cancer was ushered in by Huggins and Hodges in 1941, with the first report of an efficacious treatment for metastatic prostate cancer [1]. In this landmark report of hormonal therapy, 21 men with metastatic or locally extensive prostatic cancer were treated by orchiectomy. In 15 men, there was appreciable clinical improvement consisting of subjective improvement in appetite and decreased pain. Objectively, there was weight gain, increased red blood cell count, shrinkage of the primary tumour and increased density of metastatic bone lesions on X-ray. Additionally, these investigators were able to show that castration resulted in a sharp decrease in serum acid phosphatase and an increase followed by decrease in alkaline phosphatase. In contrast, androgen injection in 3 men caused an increase in serum acid phosphatase and worsening pain in the legs. This use of alkaline phosphatase, an enzyme with maximal activity at pH 9.5, and acid phosphatase, an enzyme with its maximal activity at pH 4.8, as biochemical markers of disease regression and progression was based on the earlier demonstration that these enzymes were elevated in the serum of patients with prostate cancer metastatic to bone [2].

Over the next 30 years, clinical trials in metastatic prostate cancer, most notably those directed by the Veterans' Administration Cooperative Urological Research Group, assessed the use of oestrogen or orchiectomy, alone, or in combination [3]. The primary response endpoints in these studies were overall survival and cause-specific survival. Comparative toxicity, a crude forerunner of quality of life (QoL) assessments, was also included. Its inclusion was due primarily to excess cardiovascular morbidity associated with diethylstilbestrol (DES).

In 1972, the National Prostate Cancer Project (NPCP) was organised, and its first co-operative trial, a comparison of 5-fluorouracil and cyclophosphamide, began in 1973 [4]. This trial was the first prospective, multicentre randomised drug trial in metastatic prostate cancer. In launching this study, one of the first challenges was to develop formal criteria for evaluating response. Several features of prostate cancer make it a difficult disease in which to assess treatment outcomes. As opposed to other solid tumours, prostate cancer metatases usually occur in bone, and the lesions are usually osteoblastic in nature. Added to this fact, dimensionally measurable soft tissue metastatic sites are uncommon and assessment of the primary disease in the prostate is difficult.

The initial studies of the NPCP focused on patients with metastases who had failed hormonal therapy and were in a state of progression at the time of entrance into a chemotherapeutic trial, now commonly referred to as hormone-refractory prostate cancer (HRPC). After registration and randomisation, patients were routinely evaluated at 12-week intervals. Response criteria were established to define complete response (a rarity), partial response, progression and stable disease [5].

Complete response (CR)

To achieve complete response a patient had to have complete disappearance of all previous cancer related abnormal areas on physical examination, e.g. hepatomegaly, and all X-rays, scans and biochemical marker studies, i.e. alkaline and acid phosphatase and liver function studies. It is important to remember that at the time these studies were being carried out prostate specific antigen (PSA) had not been developed and was not used in these definitions. If osteoblastic lesions were present, they had to disappear on bone scan, and any osteolytic lesions, if present, had to have complete recalcification. If the patient was symptomatic, he had to become asymptomatic, and there could be no significant cancer-related deterioration in weight (>10%), symptoms or performance status.

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Partial response (PR)

To be classified as a partial responder, a patient had to achieve any of the following: (1) A 50% decrease in cross-sectional area (or the sum of cross-sectional areas of both views of any bidimensionally measurable lesions; (2) reduction by 50% in the number of increased uptake areas on a bone scan; (3) recalcification of one or more of any osteolytic lesions; (4) if hepatomegaly was present, there had to be at least a 30% reduction in liver size and at least a 30% improvement of all pretreated liver function abnormalities.

Objective progression (PD)

Patients were considered to have progressive disease if any of the following were present: (1) Appearance of new areas of metastatic disease by bone scan, X-ray or by soft tissue measurement; (2) an increase in any previously measurable lesion by >25% in cross-sectional area; (3) a decrease in weight >10% and/or increase in symptoms or performance status that is related to the disease. An increase in acid or alkaline phosphatase alone was not considered an indication of disease progression.

Stable disease (SD)

The last group of disease category was one of 'stable' disease. It inferred stabilisation of the disease process. Controversy arose in that it was not known how often stabilisation would occur, albeit for a transient period, in the hormonally-refractory population of study patients. To be classified as SD, all of the following had to be present: (1) No occurrence of new lesions and no increase in measurable lesions by more than 25% in cross-sectional area; (2) if an elevated acid phosphatase was present it had to have decreased, although normalisation was not required; (3) osteoblastic lesions, if present, could not be worse on bone scan, and any osteolytic lesions could not increase; (4) as in complete responses and partial regression, there could not be any cancer-related deterioration in weight (>10%), symptoms or performance status.

PROBLEMS WITH THE NPCP RESPONSE CRITERIA

Since the introduction of the NPCP response criteria, there has been a significant increase in the number of patients diagnosed with prostate cancer and the number of patients treated on clinical trials. With this heightened focus has come increased awareness of the limitations of how we judge the efficacy of our treatments. Consequently, there is ongoing debate over the value of these original response criteria as well as that of other hard endpoints, e.g. survival. Since death may be described as the 'ultimate' endpoint, the ideal way to compare two treatment arms would be to use cause-specific death. Unfortunately, the use of cause-specific survival is problematic. Prostate cancer is a disease of the elderly and death often results from other comorbid illnesses, rather than from malignancy. Added to this problem is the unreliability of death certificates. Overall survival is most often used due to the above reasons.

Since many years may be necessary to reach conclusions based on death as the sole endpoint, soft endpoints, such as changes in radiographic abnormalities, and so-called surrogate endpoints, such as changes in biochemical markers, are used to assess treatment efficacy. It is in the area of surrogate endpoints that most debate occurs. With respect to response criteria, many investigators have questioned stable disease as a worthwhile endpoint, and its use has been all but abandoned. Others ask whether bone scans accurately assess changes in skeletal metastases or if resolution of hepatomegaly is a reliable parameter. Furthermore, in metastatic disease is prostatic acid phosphatase (PAP) worth measuring any more in the era of PSA? If the surrogate endpoint of PSA decline is included, what degree of decline in PSA, i.e. >50%, >75%, >80%, one log decline or normalisation, is of prognostic or clinical significance? Even more important, how is quality of life as an endpoint being incorporated into our response criteria? If a patient has less pain and has a renewed ability to function independently or participate in personally relevant activities, how is this measured and factored into response assessment? These are questions that are unresolved, but as they are being addressed, data are emerging to support evolving and changing response criteria.

SALVAGE STABLE DISEASE AS A RESPONSE CRITERIA

Recent investigators, especially in the arena of hormone-refractory disease, have chosen to exclude this category of stable disease, as originally defined by the NPCP. This decision may be premature and not totally justified. Certainly, in hormone-refractory prostate cancer, where therapeutic intervention has not been shown to prolong survival, a patient who remains 'stable' and is not suffering from the deleterious effects of progression is benefiting from treatment. Furthermore, using the NPCP response criteria for this group has been shown to delineate a group of patients whose survival is better than patients progressing, worse than complete responders and very similar to patients who achieve partial response [6]. Including this better prognostic group with the patients who are truly progressing will only falsely improve the survival of the latter group (the Wil Rogers phenomenon).

A BONE SCAN ALONE SHOULD NOT A RESPONSE MAKE

Greater than 90% of men with metastatic prostate cancer have bone metastases, and in the majority of cases, this bony involvement is the only documented site of distant disease. Most commonly, documentation of response in bone is assessed with a technetium polyphosphonate bone scan. However, use of bone scans to determine response is problematic for several reasons. First, bone scans may show mixed responses with some lesions appearing to improve, while others worsen. There may be variation in technique that confuses interpretation, especially when scans are performed at different institutions. Furthermore, degenerative changes, especially in the cervical spine, shoulders and hips, are common in an older population and create further problems in interpretation.

Complete responses are not difficult to assess, but are rare. Partial response rates can vary significantly based on the criteria that are used. In a subanalysis of the European Organization for Research and Treatment of Cancer (EORTC) trial 30853 comparing orchiectomy versus goserelin and flutamide in patients with metastatic disease, partial

responses based on bone scan were subdivided into those in which one area of the skeleton cleared (PR1), one or more lesions cleared (PR2), or in which there was visual improvement alone (PR3) [7]. In this analysis, the partial response rate varied from 28% for PR1 criteria to 52% for PR3 criteria. Progression is usually agreed upon by independent observers; however, the timing of progression is usually not. In this analysis, the local radiologist, who read the scan at the time it was performed, and a Bone Scan Committee, who retrospectively reviewed all available sequential scans, only agreed 7% of the time on the timing of progression. The committee diagnosed progression earlier in 32% and later in 21%, and in 40% the committee diagnosed progression when the local radiologist did not. In an analysis of EORTC trial 30762, comparing estramustine phosphate and DES response based on bone scan was of prognostic value in terms of survival, but provided little information not available from simpler prognostic factors such as anaemia, pain or performance status [8]. Pollen and colleagues had demonstrated earlier that patients whose scans showed an improvement in the number, extent or intensity of areas of increased tracer uptake had a superior median survival of 12.3 months compared to 6.3 months for patients whose scans showed worsening of these parameters [9]. Patients with stable/unchanged scans had a median survival of 15.7 months, similar to that of patients whose scans showed improvement. In this study, patients with an elevated acid phosphatase had a worse survival irrespective of the bone scan findings. Sixty-five per cent of scanning events were concordant with clinical evaluations and 35% discordant. Where there was a disagreement, discordance was secondary to the bone scan indicating progression prior to clinical evidence of progression. The one exception was a patient with a 'flare reaction'. The flare phenomenon can be an especially confusing scenario associated with increased number, intensity and size of bone lesions on bone scan, usually in the face of a patient who is clinically improving [10]. Tumour markers such as acid phosphatase may actually rise, but subsequently fall, and on serial scans improvement is demonstrated. Fortunately, flare reactions occur only in approximately 5% of truly responding patients.

One attempt to improve the interpretation of bone scans, especially intra-observer variation and differences in technique, is quantitative bone scanning [11–13]. This technique provides reliable and reproducible results, but at greater cost. Although one could more easily determine whether there has been a 50% average decrease in uptake using this method, it remains to be shown whether this information provides additional useful information compared with other simpler and less expensive prognostic determinants.

Bone scans are probably most useful under two circumstances. First, the number of 'hot spots' on an initial scan is of prognostic value with more lesions associated with shorter survival [14]. For patients enrolled in clinical trials, there should be initial stratification based on severity of bone metastases, and patients with more severe disease may preferentially be enrolled in clinical trials assessing more aggressive, investigational interventions. Second, the detection of progression on bone scan may also proceed symptoms or elevation of acid phosphatase or alkaline phosphatase [15]. Detecting patients earlier in their disease course may result in enrolment in clinical trials for HRPC at a time when they are more likely to benefit from treatment. However, with the introduction of PSA, progression on bone scan far more often lags behind an increase in PSA, by a median of 6 months [16].

NEW ENDPOINTS

Once PSA began to be used, the more-or-less accepted criteria for determining response and time to progression began to carry less significance. As mentioned, biochemical markers originally consisted of PAP, alkaline phosphatase and liver function tests. However, in the earlier trials, the elevation of PAP alone was not considered progression.

PROSTATE SPECIFIC ANTIGEN

PSA is a glycoprotein produced by prostatic epithelium. This tumour marker has had an evolving role in the diagnosis, staging and management of all stages of prostate cancer. In metastatic disease, where 98% of men have an elevated PSA, a decline in this tumour marker has been correlated with survival. PAP is elevated less frequently (77% in one comparative review) [17] and is a less sensitive indicator of response to treatment [18–20]. In patients with previously untreated advanced prostate cancer, various declines in PSA in response to endocrine therapy have been correlated with statistically significant prolonged survival. These declines include a PSA decrease to <10 ng/ml at 3–6 months, to normal (<4 ng/ml) at 1, 3 or 6 months, to nadir, to <0.5 ng/ml, by 80% or more within 1 month, by 90% or greater, or by a per cent decrease in log PSA [21–26]. In the evolving response criteria, it remains unclear what degree of decline in PSA should be required for a patient to be considered a complete or partial responder. In the interim, the response criteria vary from trial to trial and are clearly an area where consensus is needed.

In HRPC, a PSA decline of $\geqslant$50% in response to treatment, has been associated with a significantly longer median survival in patients who achieve this response compared with those who do not [27]. However, this association may be somewhat therapy specific, evidenced by the fact that it could not be confirmed on analysis of 103 patients treated with suramin [28]. Despite this variant report, most investigators accept a $\geqslant$50% decline in PSA as surrogate endpoint of disease response in this patient population, and this criterion is regularly incorporated into the response criteria for partial response. Most studies also include a decline in PSA to normal as a requirement for complete response. In HRPC, no clear consensus has been reached on the definition of progressive disease based on a rising PSA, but the most commonly accepted criterion is a >50% increase in PSA from a nadir, measured on at least three consecutive occasions over a 4-week interval (Dr N.A. Dawson, Walter Reed Army Medical Center, Maryland, U.S.A.).

Although it is generally agreed that PSA is a better tumour marker than PAP in the assessment of response to treatment, the complete abandonment of PAP is probably premature. Not only is there the uncommon, but not rare, patient in whom the PAP is elevated and the PSA is normal, but these two markers may be of additive predictive value. In a recent analysis of 107 patients with HRPC, those patients with both a >50% decline in PSA and PAP had a superior median survival of 29.6 months, compared with

those in whom only PSA declined (18.9 months) or only PAP declined (12.6 months) or when neither marker declined by >50% (8.8 months) [29].

QUALITY OF LIFE, A CRUCIAL ENDPOINT

In assessing the benefit of treatment for men with metastatic prostate cancer, it is inadequate to consider only response based on tumour shrinkage, declining PSA or even survival. Treatments that may seem equivalent based on objective response and survival, may not be equal if one considers toxicity or expense. A treatment must also be judged on its impact on quality of life, which refers to "the patient's perception of the goodness or adequacy of his existence" [30]. This definition includes the three dimensions of health outlined in the World Health Organization definition that "health is not only the absence of infirmity and disease, but also a state of physical, mental and social well-being" [31].

In 1948, Karnofsky and Burchenal pioneered the quantification of quality of life with the introduction of their performance status scale [32]. This tool simultaneously assesses activity, work and self care. However, this instrument only measures the functional aspect of quality of life. Shipper and Levitt identified that in addition to physical/occupational function, the other consistent elements of quality of life are: psychological state, sociability and somatic discomfort [33]. In order to assess these broader aspects of QoL, several questionnaires have been developed. These include the Cancer Rehabilitation Evaluation System (CARES), Functional Living Index-Cancer (FLIC), Functional Assessment of Cancer Therapy (FACT) scale, Quality of Life Index (QLI), EORTC QLQ-C30, Medical Outcomes study 36-Item Short-form health survey and linear analogue self-assessments (LASAs) [34–40]. These questionnaires are reliable, valid and sensitive and have been increasingly incorporated into prostate cancer clinical trials.

In patients with metastatic prostate cancer, impaired sexual function often plays a critical role in QoL. Hormonal therapy for metastatic disease results in sexual dysfunction in 85% of men treated with either an LHRH (luteinising hormone-releasing hormone) agonist or orchiectomy [41]. Hormonal therapy also results in other undesirable effects such as fatigue and hot flushes. Given the toxicity of treatment and the questionable impact of early hormonal therapy on survival, timing of initiation of treatment is controversial with many physicians recommending a delay in treatment until symptoms develop. In one small trial, 35 asymptomatic or minimally symptomatic men with newly diagnosed metastatic prostate cancer were offered immediate hormonal therapy versus delayed therapy when they became symptomatic. Patients receiving early therapy had greater sexual problems, fatigue and symptoms related to their medication. Psychological stress decreased after 6 months in those not receiving therapy and increased in those men being treated [42].

In the symptomatic patient, bone pain is the predominant problem, and its relief in 80% of men treated with hormonal therapy usually outweighs other toxicities of therapy. However, QoL may vary between treatment options equally capable of controlling the cancer. In one study, where men could choose either orchiectomy or monthly injections of the LHRH agonist goserelin acetate, 78% of them selected goserelin [43]. Although equally efficacious therapies in terms of tumour response, the men receiving goserelin showed substantial improvement in body image and other functional aspects of QoL as well as psychosocial status.

Intermittent androgen deprivation is a new approach to hormonal therapy in which therapy is withheld after a clinical response is achieved and is re-instituted when there is evidence of disease progression. Improvement in sexual dysfunction and improvement in sense of well-being may occur during cessation of therapy [44]. An intergroup trial has been initiated by the Southwest Oncology Group comparing continuous maximal androgen blockade (MAB) versus intermittent MAB in advanced prostate cancer looking at comparative QoL as a primary endpoint.

In clinical trials of hormone-refractory prostate cancer, where there is still no treatment that clearly prolongs survival, palliation, i.e. improved quality of life, is of paramount importance. Consequently, recent phase III trials have incorporated quality of life assessments as mandatory trial components and increasingly are considered primary study endpoints. In a recent Canadian trial, a significantly greater number of men treated with mitoxantrone and prednisone achieved pain relief than men treated with prednisone alone. The duration of pain relief was also significantly longer in the combination arm. This benefit in QoL justifies the use of this combination, despite no difference in overall survival between the treatments [45].

MOLDING THE RESPONSE CRITERIA TO THE QUESTION BEING ASKED

It seems apparent that in the evolution of response criteria for assessing new treatments for metastatic prostate cancer, one must let the question being asked dictate the response criteria employed. In the case of a phase II trial, trying to identify new efficacious therapies, declines in PSA values or shrinkage of measurable soft tissue disease may identify a treatment that deserves further assessment in a phase III setting. In a phase III trial, where the goal is to decrease pain from symptomatic bone metastases, the primary endpoint will be improvement based on various assessments of pain such as analgesic use or improvement on a particular pain scale. For trials comparing combinations very likely to be equivalent in terms of tumour response and survival, such as the intermittent versus continuous androgen deprivation, assessment of quality of life that quantifies the relative impact of symptoms of disease and side-effects from treatment are the critical element.

CHANGING ENDPOINTS

Unfortunately, responses may be discordant. A patient may have a decline in PSA, but no objective shrinkage of tumour masses. The patient may have less pain, but the PSA may rise. Additionally, shrinkage of tumour masses, a decline in PSA or improvement in QoL may have no impact on survival. To improve the assessment of the benefit of a given therapy, it may be far more useful to abandon the traditional standard response criteria of CR, PR, SD and PD and instead to report separately responses in bone, measurable disease, symptoms and biochemical markers. For bone disease, given the difficulty in quantifying changes, it may be best to classify response as improved, unchanged or

worse. For measurable disease, the continued use of standard phase II response criteria is recommended. Hepatomegaly is far too nebulous and difficult to quantify and should not be included. The use of established, reliable and valid QoL questionnaires, to include those specific to prostate cancer, pain scales and performance status, should be mandatory for all clinical trials in metastatic prostate cancer and should also be reported separately. Until a consensus can be reached regarding what degree of PSA decline is significant, reporting the number and per cent of patients with a >50%, >80% decline and normalisation of PSA should be included.

Criteria for progression should also be broken down, i.e. rising PSA, new lesions on bone scan or new cancer-related symptoms. Although impact on survival is considered by most investigators to be the endpoint most likely to influence their treatment practice and should be included in all trial reports, other endpoints are equally important from the patient's perspective. In a 1995 survey of 1000 members of the U.S. TOO prostate cancer support group, 85% of men listed slowing their cancer and extending their life as what they wanted from prostate cancer treatment [46]. However, this was not appreciably different from the desire for improved quality of life, which 81% rated as important. Finally, consensus on response criteria is crucial in determining the comparative efficacy of the different treatments being assessed in metastatic prostate cancer. Investigators active in this area of research need to formalise new response criteria that incorporate the changing dimensions of metastatic prostate cancer.

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