Treatment of Hormone-Refractory Prostate Cancer with Docetaxel or Mitoxantrone: Relationships between Prostate-Specific Antigen, Pain, and Quality of Life Response and Survival in the TAX-327 Study

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Abstract

Purpose: The TAX-327 study randomized 1,006 men with metastatic hormone-refractory prostate cancer to receive 3-weekly docetaxel, weekly docetaxel, or mitoxantrone, each with prednisone.

Experimental Design: We used the TAX-327 database to address (a) the relationship between quality of life (QoL) and pain; (b) whether minimally symptomatic patients benefit from treatment or have treatment-related decline in QoL; (c) the relationships between prostate-specific antigen (PSA) response, pain response, and QoL response; (d) the times at which these responses are first observed; and (e) whether PSA, pain, and/or QoL response predict for overall survival.

Results: At baseline, 374 of 815 men assessed for QoL had major pain; of these, 92% had substantial impairment of QoL compared with 75% without major pain (P < 0.001). Men with minimal symptoms had prolonged survival (median, 25.6 months) compared with symptomatic patients (median, 17.1 months; P = 0.009); they were more likely to have initial deterioration of QoL if treated with weekly docetaxel. PSA response and pain response, but not QoL response, were independently associated with survival in landmark analysis. Median times to PSA and pain response were 44 and 27 days, respectively; some men had initial increase in serum PSA before subsequent decline.

Conclusions: Symptoms other than pain contribute to impaired QoL in men with hormone-refractory prostate cancer. Those with minimal symptoms have prolonged survival. Both pain and PSA response are associated with survival but are not adequate to use as surrogate end points in phase 3 studies. Early increases in serum PSA (up to 12 weeks) should be ignored when determining response or progression.

Metastatic prostate cancer is an incurable disease and the goal of treatment is palliation. Hormonal treatment is effective initially, but after a variable time, prostate cancer progresses to a hormone-refractory state. Many men then receive chemotherapy with the goals of alleviating symptoms and prolonging survival. The TAX-327 study was a large international randomized trial, which compared the effectiveness of 3-weekly mitoxantrone and prednisone (M/P) with 3-weekly docetaxel and prednisone (D3/P) or weekly docetaxel and prednisone (D1/P) for men with hormone-refractory prostate cancer (1). The primary end point of the study was overall survival, whereas pain response, prostate-specific antigen (PSA) response, and quality of life (QoL) response were secondary end points. Men treated with docetaxel every 3 weeks with prednisone were found to have superior overall survival, pain response, PSA response, and QoL response when compared with those receiving mitoxantrone and prednisone (1).

Here, we have examined the database from the TAX-327 study to provide an in-depth analysis of the relationships between PSA response, pain response, QoL response, and survival. We attempt to address the following questions:

1. What is the relationship between QoL and pain?
2. Do men with minimal symptoms benefit from treatment or does treatment-related toxicity lead to a decline in QoL?
3. What is the interrelationship between PSA response, pain response, and QoL response? At what times after initiation of treatment are these responses first observed?
4. Do PSA, pain, and/or QoL response predict for overall survival?
Materials and Methods

Details of participants and their treatment are described in the original report of the trial (1). In brief, the TAX-327 study was an international, randomized, three-arm study that included men with progressive metastatic hormone-refractory prostate cancer. They were randomized to the following three arms: docetaxel (75 mg/m²) every 3 wk (n = 335), weekly docetaxel (30 mg/m²) for 5 of every 6 wk (n = 334), or mitoxantrone (12 mg/m²) every 3 wk (n = 337). All men received 5 mg prednisone twice daily or equivalent.

PSA levels were measured at baseline and every 3 wk during treatment, and men with a serum level of PSA ≥20 ng/mL at baseline were evaluated for PSA response. PSA response required ≥50% reduction in serum PSA from baseline, maintained for at least 3 wk. PSA progression was defined by ≥25% increase over nadir in men with PSA response and ≥50% in nonresponders.

At 3-weekly intervals, participants rated their average pain level with the use of the present pain intensity (PPI) scale from the McGill-Melzack questionnaire (2). The PPI varies between 0 and 5 with verbal descriptors; higher numbers indicate greater pain. The daily analgesic intake was recorded and an analgesic score (AS) was calculated by assigning four points for a standard dose of narcotic medication and one point for a standard dose of nonnarcotic pain medication. Pain levels were required to be stable for at least 7 d before randomization. Pain response was evaluated in men with PPI ≥2 and/or AS ≥10 at baseline and was defined by ≥2-point reduction in PPI with no increase in AS or ≥50% reduction in AS with no increase in PPI, maintained for at least 3 wk.

QoL was rated by the self-administered Functional Assessment Cancer Therapy—Prostate (FACT-P) questionnaire (3, 4) at baseline and every 3 wk during treatment and monthly on follow-up. The FACT-P score is composed of 22 general questions about physical, social, emotional, and functional well-being as well as a 17-item questionnaire about prostate-specific concerns. It is available in multiple languages and was completed by men in the trial if it was available in the local language. A maximum score of 156 points indicates the highest level of QoL; QoL response was defined in the protocol by ≥10% (16 points) increase in the FACT-P score maintained for at least 3 wk. A 16-point (≥10%) decrease in the FACT-P score was used here to identify deterioration in QoL.

For the current analysis, participants were defined as being minimally symptomatic at baseline if they had a FACT-P score >128 (i.e., within 20% of a “perfect” QoL score) and PPI <2 and AS <10 (men identified as having minimal pain in the original protocol).

Statistical analysis. All analyses are considered exploratory and were undertaken after the primary analysis was reported (1). Exact P values are reported throughout and all tests were two sided. No correction has been made for multiple comparisons.

Associations between PSA response, QoL response, pain response, and survival were investigated for all participants that could be assessed for these attributes and also by individual study arm. Associations between the proportions of men with impaired QoL and pain at baseline were investigated after combining data from all three cohorts. To reduce the bias that associations between response rates (and between response rates and survival) might occur because participants with any type of response remain on treatment for longer periods (and hence have a higher chance of other types of response and of longer survival), time-dependent landmark analyses of on-study associations were done (5). A landmark analysis takes a particular landmark time point and renurs the analysis using that date as the new day 1. Any events, which occur before the landmark time point, are excluded from the landmark analysis. Covariates are evaluated by whether the particular covariate has occurred before that landmark. For example, if ≥2 mo is chosen as the landmark date, then when evaluating if response is predictive of survival a patient having a response before 2 mo would be counted as response = no, whereas a patient having a response first observed after 2 mo would be counted as response = yes. Landmark times of 0, 2, 3, 4, and 6 mo were chosen.

The effects of treatment on minimally symptomatic men were investigated by the PSA, pain, and QoL response rates and overall survival between treatment arms as well as by the differences in overall survival between minimally symptomatic patients and all men included in the trial.

Associations between response rates were evaluated by the Mantel-Haenszel test stratified by treatment. Survival outcomes were evaluated using Cox proportional hazards regression.

Results

The TAX-327 study recruited 1,006 men in 24 countries from March 2000 to June 2002. Baseline characteristics of the three groups were similar in terms of age (median, 68), Gleason score (77, ~40%); 8-10, 30%; remainder unknown), prior hormonal manipulations, Karnofsky performance status, pain (45% could be assessed for pain response), serum PSA (median, 115 ng/mL; 87% could be assessed for PSA response), and extent of disease. QoL was assessed in 815 of 1,006 participants.

The database used to evaluate different categories of response was established in August 2003 and described in the original publication (1). Data for survival are based on a recent update (March 2007: 867 of 1,006 participants now known to have died; ref. 6): in brief, differences between the arms have been maintained with median survival duration of 19.2 months for the D3/P arm (P = 0.004, compared with M/P), 17.8 months for the D1/P arm (P = 0.17, compared with M/P), and 16.3 months for the M/P arm.

Association of pain and QoL. Of 815 men who completed the FACT-P at baseline, 374 (46%) had substantial pain (PPI ≥2 or AS ≥10); of these, 345 (92%) also had substantial impairment of QoL (FACT-P score ≤128). Of the 441 men who did not have substantial pain at baseline, 331 (75%) had FACT-P score ≤128. This difference is statistically significant (P < 0.001), although it is evident that symptoms in addition to pain contribute to impaired QoL.

Men with minimal symptoms. There were 110 men who were minimally symptomatic at baseline, as defined by FACT-P score >128, PPI <2, and AS <10. More of these men were randomized to the mitoxantrone arm (n = 48) than the D3/P (n = 29) or the D1/P (n = 33) arms. Median survival for minimally symptomatic men was 25.6 [95% confidence interval (95% CI), 21.6-28.4] months compared with 17.1 (95% CI, 16.2-18.3) months for more symptomatic patients (P = 0.009). The median survival for minimally symptomatic patients was 28.4, 25.9, and 22.0 months for D3/P, D1/P, and M/P, respectively. Differences in survival between treatment arms among minimally symptomatic patients reflected the differences observed in the whole group, although they did not reach statistical significance due to small numbers.

Deterioration and response in QoL. Overall, 81 of 278 (29.1%) men in the D3/P arm, 101 of 270 (37.4%) in the D1/P arm, and 68 of 267 (25.5%) in the M/P arm experienced QoL deterioration on treatment (P = 0.39 and 0.003 for comparison with M/P). Because there was a possible bias that men treated for longer periods would be more likely to have QoL deterioration, the analysis was repeated with participants stratified by duration on study (<120 versus ≥120 days); this analysis gave similar findings (P = 0.25 for D3/P versus M/P and P = 0.091 for D1/P versus M/P). Among minimally
symptomatic men, 41.4% D3/P, 51.5% D1/P, and 27.1% M/P had deterioration in QoL (Fig. 1).

The 441 men without major pain at baseline (PPI <2 and AS <10) and who completed FACT-P at baseline were evenly distributed among the three treatment cohorts. Among these men, 18.8% in the D3/P arm (P = 0.05, compared with M/P), 18.5% in the D1/P arm (P = 0.07, compared with M/P), and 10.3% in the M/P arm had a QoL response, whereas 31.5% in the D3/P arm, 43.2% in the D1/P arm, and 28.8% in the M/P arm had a QoL deterioration (Fig. 1).

**Association of PSA response with pain and QoL response.** There were 414 men assessed for both pain response and PSA response: PSA response was seen in 52.4% of 124 men (53% of D3/P, 71% of D1/P, and 23% of M/P) with pain response and in 28.3% of 290 men (25% of D3/P, 37% of D1/P, and 24% of M/P) without pain response (P < 0.001; Fig. 2).

There were 704 men evaluable for both QoL response and PSA response: PSA response occurred in 56.5% of 147 men (57% of D3/P, 69% of D1/P, and 34% of M/P) with QoL response and 37.5% of 557 men (41% of D3/P, 40% of D1/P, and 33% of M/P) without QoL response (P < 0.001; Fig. 2).

**Association of PSA, pain, and QoL response with survival.** A total of 873 men (87% of all participants) were evaluable for PSA response, which was observed in 45.4% (D3/P), 47.9% (D1/P), and 31.7% (M/P; P < 0.001, for comparison of either docetaxel arm with the mitoxantrone arm; ref. 1). Median survival for those with and without PSA response is shown in Fig. 3A for all participants and by treatment assignment. Men with PSA response lived significantly longer than men without PSA response [hazard ratio (HR), 0.45; 95% CI, 0.39-0.53; P < 0.001]. Landmark analysis confirmed that PSA response remained a predictor of survival beyond different time points (Table 1).

Median survival and 95% CIs for men with and without QoL response are shown in Fig. 3C for all participants and by treatment assignment. After adjusting for PSA and pain response, QoL response was not a significant predictor of survival (HR, 0.97; 95% CI, 0.74-1.28; P = 0.84).

**Time to PSA, pain, and QoL response.** The median number of days (with interquartile range) to first observation of PSA, pain, and QoL response is 44 (26-68), 27 (22-49), and 43 (23-85) days, respectively, and was similar among the treatment arms (Table 2). The percentage of subjects who had transient worsening of these end points before going on to satisfy criteria of response were 16.7%, 23.7%, and 27.4%, respectively. For the QoL end point, 1.9% of participants had a decrease of >16 points in FACT-P score (i.e., met criteria for deterioration of QoL) before going on to respond with ≥16-point increase compared with baseline.

There were 80 men (22 D3/P, 32 D1/P, and 26 M/P) who had an increase in their serum PSA after starting treatment, but insufficient to satisfy criteria of PSA progression, and later had a PSA response. We were also able to identify 23 men (10 D3/P, 10 D1/P, and 3 M/P) who satisfied criteria of PSA progression but later had at least one PSA measurement, which was <50% of the baseline value; this is a minimum estimate of the total number of such participants because others who were classified as having early progression may have changed treatment and/or not have subsequent PSA values available. These latter 23 men would not have been counted as PSA responders. Considering all participants with PSA data, 50% of PSA responses occurred within the first two cycles and 80% within the first four cycles (i.e., 12 weeks) of chemotherapy.

**Discussion**

Men with metastatic hormone-refractory prostate cancer may have a variety of symptoms that lead to reduced QoL. Our analysis of the TAX-327 database revealed that most participants had impaired QoL at baseline even in the absence of substantial pain. Other symptoms related to prostate cancer,

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**Fig. 1.** QoL deterioration for all patients and for minimally symptomatic patients (P values compared with M/P).

**Fig. 2.** Relationship between pain response and PSA response, as well as QoL response and PSA response.
including fatigue, and effects of specific (e.g., hormonal) and supportive treatments can negatively affect QoL of men with prostate cancer. Both QoL and pain can be improved by chemotherapy.

An important question for a man with progressive hormone-refractory prostate cancer but minimal symptoms is whether to initiate chemotherapy or to wait until symptoms occur. Although chemotherapy may halt or reverse progression of prostate cancer, associated toxicity might lead to deterioration of QoL. Not surprisingly, we found that men with minimal symptoms had prolonged survival compared with all participants, but this does not necessarily imply benefit from early use of chemotherapy. Some men had decreased QoL after starting chemotherapy, and this was more often observed in men with minimal symptoms and more likely to occur in patients that received weekly docetaxel. The use of docetaxel every 3 weeks, which generally has more toxicity than mitoxantrone, was not associated with significantly greater deterioration of QoL, presumably because added toxicity was counterbalanced by greater effects to delay progression of disease.

Possible reasons why weekly docetaxel led to a small but significant increase in the probability of deterioration of QoL include more frequent hospital visits, which might be stressful for elderly men. There is also a potential bias in the assessment of QoL for men receiving weekly treatment because men treated every 3 weeks are more likely to have recovered from acute toxicity at the time of completion of the FACT-P questionnaire than those treated 1 week previously, although the limiting toxicity of both docetaxel and mitoxantrone is more often due to chronic than acute effects. Weekly docetaxel was originally included as an arm in the study because it was expected to be better tolerated by elderly men. However, except for reduced myelosuppression, which rarely was clinically important, weekly docetaxel was less effective than the 3-weekly schedule (1, 6) and more likely to reduce QoL. This schedule should be used only in exceptional circumstances, for example, in men with compromised bone marrow reserve who are at high risk of septic neutropenia.

In the TAX-327 study, there were significant correlations between PSA response and both pain and QoL response. Possible reasons why weekly docetaxel led to a small but significant increase in the probability of deterioration of QoL include more frequent hospital visits, which might be stressful for elderly men. There is also a potential bias in the assessment of QoL for men receiving weekly treatment because men treated every 3 weeks are more likely to have recovered from acute toxicity at the time of completion of the FACT-P questionnaire than those treated 1 week previously, although the limiting toxicity of both docetaxel and mitoxantrone is more often due to chronic than acute effects. Weekly docetaxel was originally included as an arm in the study because it was expected to be better tolerated by elderly men. However, except for reduced myelosuppression, which rarely was clinically important, weekly docetaxel was less effective than the 3-weekly schedule (1, 6) and more likely to reduce QoL. This schedule should be used only in exceptional circumstances, for example, in men with compromised bone marrow reserve who are at high risk of septic neutropenia.

In the TAX-327 study, there were significant correlations between PSA response and both pain and QoL response.

<table>
<thead>
<tr>
<th>Time point</th>
<th>HR for PSA response (95% CI)</th>
<th>P</th>
<th>HR for pain response (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.45 (0.39-0.53)</td>
<td>&lt;0.001</td>
<td>0.59 (0.47-0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 mo</td>
<td>0.58 (0.49-0.69)</td>
<td>&lt;0.001</td>
<td>0.70 (0.56-0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.52 (0.44-0.60)</td>
<td>&lt;0.001</td>
<td>0.68 (0.54-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 mo</td>
<td>0.48 (0.41-0.55)</td>
<td>&lt;0.001</td>
<td>0.64 (0.51-0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.46 (0.40-0.54)</td>
<td>&lt;0.001</td>
<td>0.60 (0.48-0.74)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
However, there is a substantial proportion of patients that achieve PSA response but do not seem to obtain palliative benefit, at least as measured by reduction in pain or analgesic intake or by improved QoL. PSA response is weakly associated with palliative response in other studies (7). In clinical practice, PSA is measured accurately and easily, whereas QoL is generally not assessed, and the available QoL questionnaires have only been validated for use in clinical trials. Therefore, most physicians base their decision about continuing treatment on a general impression of the patient’s well-being and on their PSA kinetics; failure to evaluate QoL response might sometimes lead to suboptimal clinical decisions.

Surrogate markers have been of limited value in predicting survival in phase III trials for men with prostate cancer. In the present analysis of the TAX-327 study, both PSA response and pain response were found to be associated with longer survival. These associations remained valid in landmark analyses that were undertaken to minimize the bias that longer surviving participants have more opportunity to manifest response (5). QoL response was not associated with longer survival. These results are in line with findings from other authors (8–10). In a recent analysis based on the large Southwest Oncology Group 99-16 trial, a decline in serum PSA of 30% and posttreatment PSA velocity were shown to be meaningful surrogate markers for survival (11), but these results require confirmation.

In our study, pain response was a powerful independent predictor of survival, even when accounting for PSA response; this is an important finding as pain response is a co-primary goal in palliation, whereas PSA response is not an end point of palliation (except in as far as it reduces anxiety). However, neither PSA nor pain response can substitute for overall survival as a primary end point in future phase 3 studies. A detailed analysis of PSA surrogacy and survival based on the TAX-327 trial has been published recently (12).

In this analysis, PSA response did not precede pain or QoL response. Thus, the serum marker does not anticipate the palliative benefit of chemotherapy. Interestingly, the database includes 80 patients that had rising PSA, which did not fulfill the criteria of progressive disease, who then achieved a PSA response at a later time. We identified 23 patients with initial PSA increase that fulfilled criteria of progression but later had a decline of at least 50% in serum PSA compared with baseline. There may be additional patients who would have “responded” if their treatment had not been stopped or changed soon after randomization because of PSA progression (13). These data reflect the importance of not discontinuing chemotherapy too early and we now recommend administering at least four cycles of chemotherapy (i.e., continuing for at least 12 weeks) unless there is major clinical deterioration or toxicity.

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### References

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