



# EVIDENCE WATCH

## A review and assessment of recent clinical trial data

This issue of *Oncology Exchange* provides overviews of important clinical trial data originally presented at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in New Orleans, LA, June 5-9, 2004. Leading Canadian experts offer commentary and clinical interpretations.

### Prostate cancer

#### DOCETAXEL PLUS PREDNISONE OR MITOXANTRONE PLUS PREDNISONE FOR ADVANCED PROSTATE CANCER

Investigators: I.F. Tannock et al.  
Journal: *NEJM* 2004;351:1502-12

The TAX 327 Study was a randomized, nonblinded, Phase 3, international, multicentre trial conducted in 1006 men with metastatic hormone-refractory prostate cancer. Enrolled patients had testosterone level < 50 ng/mL, adequate physiologic, clinical and PSA evidence of disease and had stopped taking antiandrogens within the prior 6 weeks. They were randomized to receive 5 mg of prednisone twice daily plus 1 of 3 treatment schedules: docetaxel 75 mg/m<sup>2</sup> q 3 weeks for 10 weeks, 30 mg/m<sup>2</sup> docetaxel per week for 5 of 6 weeks over 5 cycles, or mitoxantrone 12 mg/m<sup>2</sup> q 3 weeks for 10 cycles.

After an average followup of 20.7 months, median overall survival (the primary endpoint) was 18.9 months in the docetaxel + prednisone group, 17.4 months in the weekly docetaxel group and 16.5 months in the mitoxantrone group (Table 1), with 166, 190 and 201 deaths respectively. More men in the docetaxel groups — 45% of those receiving 75 mg/m<sup>2</sup> q 3 weeks and 48%

**TABLE 1. Outcomes in 1006 men with metastatic hormone-refractory prostate cancer**

	Docetaxel q 3 wks + prednisone (n = 335)	Docetaxel weekly + prednisone (n = 334)	Mitoxantrone + prednisone (n = 337)
Median survival	18.9 months	17.4 months	16.5 months
PSA reduction*	45%	48%	32%
Pain reduction†	35%	31%	22%

\*Percent of patients achieving PSA reduction of ≥ 50% for ≥ 4 weeks

† Percent of patients achieving pain reduction

in of those receiving 30 mg/m<sup>2</sup> weekly — achieved at least 50% decreased serum PSA levels for 4 weeks, as compared with 32% in the mitoxantrone group (P < 0.001). Differences in pain response, as determined by Present Pain Intensity and analgesic usage scores, were significant between the q 3-weekly docetaxel group vs the mitoxantrone groups (35% vs 22%, P = 0.01) but not between the weekly docetaxel and mitoxantrone groups. Quality of life,

evaluated using the FACT-P questionnaire in 815 patients, improved significantly in patients receiving docetaxel compared the others. Patients in the docetaxel groups had a higher rate of low-grade side effects: 26%, 29% and 20% in the 3 groups, respectively. The authors conclude that cytotoxic chemotherapy conferred a survival advantage, with the q 3-weekly docetaxel + prednisone regimen showing the best results in this study.

**DOCETAXEL AND ESTRAMUSTINE COMPARED WITH MITOXANTRONE AND PREDNISONE FOR ADVANCED REFRACTORY PROSTATE CANCER**

**Investigators: D.P. Petrylak et al. NEJM 2004;351:1513-20.**

The Southwest Oncology Group (SWOG) Intergroup protocol 99-16 was a prospective, randomized, Phase 3 trial in 770 men with advanced androgen-independent prostate cancer. Patients with ongoing Stage 4 (or D1–D2) disease despite androgen-ablative therapy were randomized to 2 arms receiving 21-day treatment cycles as follows:

- 280 mg estramustine 3 x/day 1 hour before or 2 hours after meals on Days 1 through 5 + 60 mg/m<sup>2</sup> docetaxel on Day 2, and 60 mg dexamethasone in 3 divided doses before docetaxel (n = 338)
- 12 mg/m<sup>2</sup> mitoxantrone on Day 1 + 5 mg of prednisone twice daily (n = 336)

In the absence of Grade 3 or 4 adverse events, doses of docetaxel and mitoxantrone were increased to 70 mg/m<sup>2</sup> and 14 mg/m<sup>2</sup>, respectively, during the first cycle.

After 32 months of followup, median overall survival was 17.5 months in the estramustine + docetaxel + dexamethasone group and 15.6 in the mitoxantrone + prednisone group (P = 0.02) (Table 2). The corresponding hazard ratio for death was 0.80 (95% CI 0.67

**TABLE 2. Outcomes in 770 men with Stage 4 androgen-independent prostate cancer**

	Estramustine + docetaxel + dexamethasone (n = 338)	Mitoxantrone + prednisone (n = 336)	P-value
<b>Efficacy measures</b>			
Median overall survival	17.5 months	15.5 months	P = 0.02
Time to progression	6 months	3.2 months	P < 0.001
PSA reduction ≥ 50%	50%	27%	P < 0.001
<b>Incidence of adverse events</b>			
Cardiovascular	15%	7%	P = 0.001
Nausea and vomiting	20%	5%	P < 0.001
Metabolic disturbances	6%	1%	P < 0.001
Neurologic	7%	2%	P = 0.001
Grade 3–4 neutropenia	5%	2%	P = 0.01

to 0.97). The docetaxel group also had a superior median time to progression of 6.3 months, compared to 3.2 months in the other group (P < 0.001). They also had more frequent reduction in serum PSA levels: 50% vs 27%, respectively, showed a decline of at least 50% (P < 0.001). Measurable tumour response rates were 17% vs 11% respectively, but the difference was not statistically significant (P = 0.30). Patients receiving estramustine + docetaxel +

dexamethasone, however, experienced more frequent cardiovascular events, nausea and vomiting, metabolic disturbances, neurologic events and higher rates of Grade 3 or 4 neutropenic fever (Table 2); there were 8 and 4 treatment-related deaths, respectively. Thus, the authors conclude, the survival benefit conferred by the docetaxel combination comes at the cost of increased side effects.

**COMMENTARY: Fred Saad, MD, FRCSC, Director of Urologic Oncology, Centre Hospitalier de l'Université de Montréal; Professor, Department of Surgery/Urology, Université de Montréal.**

Hormone-refractory prostate cancer (HRPC) has been a difficult challenge ever since hormone therapy was determined to be of use. Most clinicians adopted a purely palliative plan in treating hormone-refractory patients. Several chemotherapeutic regimens were tried over the years, but showed disappointingly low response rates and no survival advantage. The advent of mitoxantrone finally provided evidence that chemotherapy could play a role in managing the severe pain and diminished quality of life that accompanies metastatic HRPC, and gave something to offer beyond painkillers and palliative radiotherapy. Evidence that chemotherapy could prolong survival, however, was lacking.

The 2 trials that were presented at the 2004 ASCO meeting,<sup>1,2</sup> and recently reported in the *New England Jour-*

*nal of Medicine*, compared docetaxel-based regimens to the approved mitoxantrone regimen. The main endpoint measured improvement in survival. Secondary endpoints — related to PSA reductions, pain control and quality of life — are also extremely important. These trials also addressed whether it is better to give docetaxel weekly or every 3 weeks, and whether estramustine phosphate improves results.

**LONGER SURVIVAL WITHOUT ADDITIONAL TOXICITY**

Results for the first endpoint regarding overall survival were positive and showed that docetaxel given every 3 weeks afforded a significant survival advantage in both

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## LANDMARKS

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studies. This in itself is very significant since it is the first time any chemotherapy regimen has improved survival in HRPC, and the survival improvements compare favourably with those achieved in Phase 3 studies of chemotherapy in other metastatic cancers such as breast cancer. The advantage was achieved even when compared to a chemotherapy regimen that has some undeniable biologic activity — mitoxantrone is not placebo. Patients who had progressed on mitoxantrone were allowed to switch to treatment with docetaxel, possibly improving mitoxantrone's efficacy in the intent to treat analysis. The average survival in the range of 18 months, longer than in previous studies looking at metastatic HRPC, suggests that patients are being treated earlier — and this is also reflected by the significant number who entered the study without pain.

Survival is important but at what price? The longer survival was accompanied by significant improvements in pain control, PSA response and quality of life. Toxicity profile is another important element when considering chemotherapy: reassuringly, serious toxicity with docetaxel was no higher than with mitoxantrone, and the 3-weekly dose of docetaxel was associated with no more significant toxicity than was weekly docetaxel.

Adding estramustin did not improve survival but was associated with more toxicity. In my opinion no convincing evidence supports its use in HRPC, and these studies further confirm that if docetaxel is to be used in combinations, a different drug is needed.

## A NEW ERA

Now that we have active therapies on which to build, it is a very exciting time to be working in the field of HRPC — and a great opportunity for urologists and oncologists to create a team approach. Many urologists have been reluctant to refer patients since there was really not much to offer, and likewise, oncologists were not enthusiastic to see prostate cancer patients given the lack of active treatment options. Zoledronic acid was recently shown to significantly reduce complications related to bone metastases in HRPC, similar to the results obtained in women with metastatic breast cancer.<sup>3</sup> Preclinical evidence implies synergy between zoledronic acid and docetaxel which hopefully will translate to even better patient outcomes. Future research building on these results will work in several ways to further improve our approach to advanced prostate cancer. More work will continue in HRPC to find combinations with novel agents to achieve better survival. Chemotherapy will be introduced earlier in the prostate cancer continuum, in metastatic hormone-sensitive disease (where progression to HRPC is only a question of time), in high-risk non-metastatic HRPC patients and in those with high-risk localized cancer.

Despite inability to cure advanced prostate cancer, studies have demonstrated that early hormone therapy improves survival and, now, that chemotherapy provides further efficacy. Thus we can approach prostate cancer as a

chronic disease — we have something to offer at the different stages to improve survival and quality of life. **CE**

## References

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