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Contents

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ANDROGEN INSENSITIVE DISEASE: Chemotherapy For Hormone Refractory Prostate Cancer: The Context and the New Content

A familiarity with the natural history of hormone refractory prostate cancer (HRPC) gives perspective for placing the results of the recently reported chemotherapy trials into their full context. The classic contribution that describes this "context" was the analysis by Drs. Pound, Partin, Eisenberger and Walsh in JAMA, 1999, Vol 281: "Natural history of progression after PSA elevation following radical prostatectomy". In a trial that could probably never be repeated, 1997 men who had a PSA recurrence of > 0.2 ng/mL were followed *without therapy* until the appearance of metastatic disease which developed at a median of about 8 years. Factors that adversely hastened the time to metastases were Gleason score ≥ 8, PSA recurrence earlier than two years post surgery, and PSA-DT of <10 months. Androgen deprivation was effected at this point, and the median time to death was about 5 years. (See Figs 1,2.) This interval was progressively longer if the metastases occurred at 1-3, 4-7, or > 8 years after surgery.

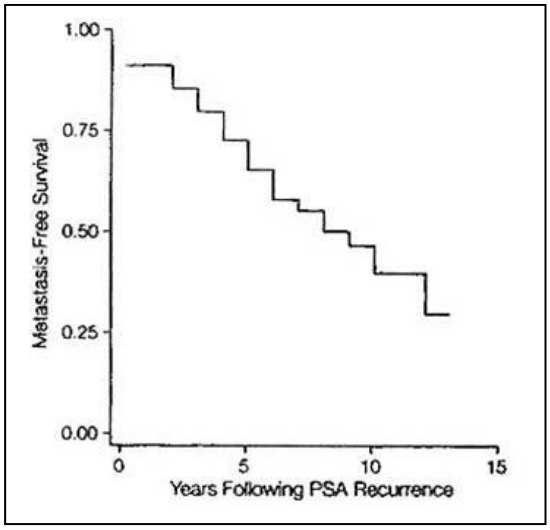

Figure 1

A second informative "natural history" analysis came from Oefelein et al, J Urol April 2004: "Survival of

patients with hormone refractory prostate cancer in the prostate specific antigen era". The study identified 254 men with HRPC enrolled in phase II and III clinical trials and determined the time from PSA elevation of > .3 ng/mL to death. The *median survival* of the men who entered this period of HRPC with a positive bone scan was 40 months, and for those without bone scan evidence of metastases, 68 months. For all men in the study the median survival was about 4 1/2 years. Oefelein's conclusion was that the "historically reported survival of 12 to 18 months after HRPC develops requires clarification and revision". He observed that trials conventionally calculate survival from the date of enrollment, and that "this convention truncates the duration of survival because the patients enrolled are frequently far along in the hormone refractory disease course," as was the case in the two recent trials that will be discussed next.

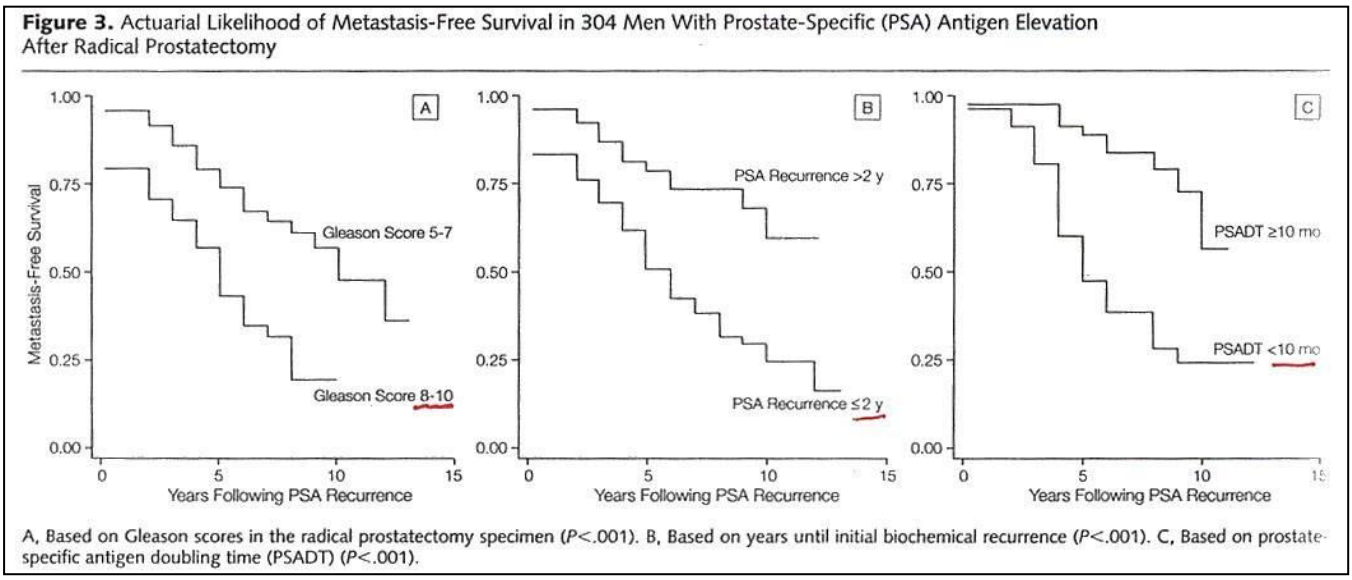

Figure 2

In the October 7, 2004 issue of the NEJM two major phase III chemotherapy trials were reported for men with HRPC. The Tax-327 trial compared two regimens of docetaxel/prednisone to mitoxanthrone/prednisone and reported a median survival for the weekly docetaxel regimen at 17.4 months, for q 3 week docetaxel - 18.9 months, and for mitoxanthrone - 16.5 months (docetaxel arms vs. mitoxanthrone significant at P=0.05). In the SWOG 99-16 trial the combination of docetaxel/estramustine (D/E) showed a median survival of 17.5 months compared to the mitoxanthrone/prednisone (M/P) arm, 15.6 months (P=0.02). Supporting Oefelein's observation, however, these trials enrolled patients that were "far along in the hormone refractory disease course". The median PSA values at entry for the Tax-327 study were 108,114,123 ng/mL and 90% of men had a positive bone scan. For the SWOG trial the median entry PSA was 87 ng/mL and ~ 85% of men were bone scan positive.

The percent of trialists who achieve a PSA reduction of greater than 50% is a common parameter of comparison between studies. In the Tax trial a better than 50% PSA reduction was seen in 45%-48% of men compared to the mitoxanthrone arm, 32%. In the SWOG trial the percentage showing more than 50% PSA reduction for docetaxel/estramustine was 50% vs. 27% for the mitoxanthrone arm. However, Dr. Eisenberger and others have pointed out that comparisons based on PSA reductions can be misleading. He has argued that the important comparative observation regarding trial outcomes is the median time to disease progression (TTP), which, interestingly, is about 5 to 6 months in all of the recent trials employing, as they did, a variety of agents. This similarity in TTP suggests that each of the regimens interrupted the ultimate progression of the disease to the same extent. A treatment regimen that exacts greater toxicity without producing improvement in "time to disease progression" may not be conferring a benefit commensurate with toxicity despite showing a superior percent of PSA reduction or a longer median survival, or even a modest increase in overall survival in comparison with a regimen with an equivalent

TTP and less toxicity. This consideration calls into question the use of estramustine, since its inclusion in a regimen adds significantly to toxicity.

The statistically unsophisticated person reading the media announcements reporting that chemotherapy now confers a "survival benefit" might easily be excused for thinking that all persons receiving the "better" treatment would enjoy a comparatively longer life, (i.e., the SWOG trial showed a two month prolongation in median survival). In fact, the maximal comparative survival benefit of two months is only "realized" by a man dying at the median point of the curve compared to a man dying simultaneously at a parallel point on the curve of the alternative trial arm. With increasing time beyond the mid-point of the curves the comparative survival benefit progressively decreases until at about 4 years there is no survival benefit between the treatment arms and all the men had died. Figure 3 below shows data from SWOG 99-16 that illustrates this point.

Figure 4 displays "progression-free survival" for SWOG 99-16, in an analysis often described as a "time to progression" curve. A typical "*duration* of PSA response" to chemotherapy may be 3 to 4 months, and the "*time to disease progression*" - in this study a median time of 6.3 months for the D/E arm from the start of therapy to the point of PSA progression - is the sum of the response duration (if any) and the additional time required to return to the pre-response PSA value. There is no evidence that a tumor's growth rate changes after a temporarily successful chemotherapeutic intervention. Since all trialists ultimately showed progression by about 36 months, it could be said that the D/E regimen effected a comparatively longer "postponement of progression" than M/P.

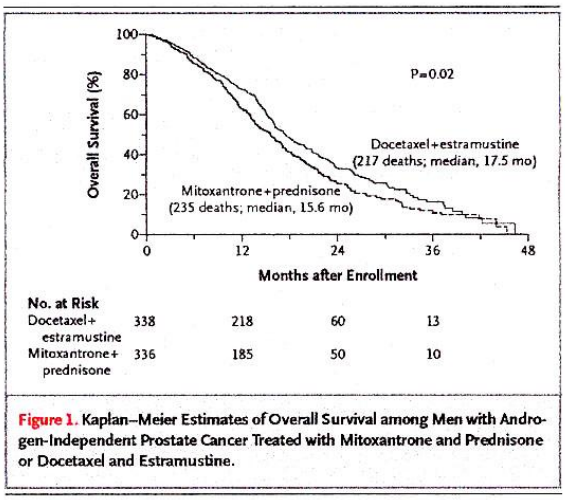

Figure 1. Kaplan–Meier Estimates of Overall Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

Figure 3

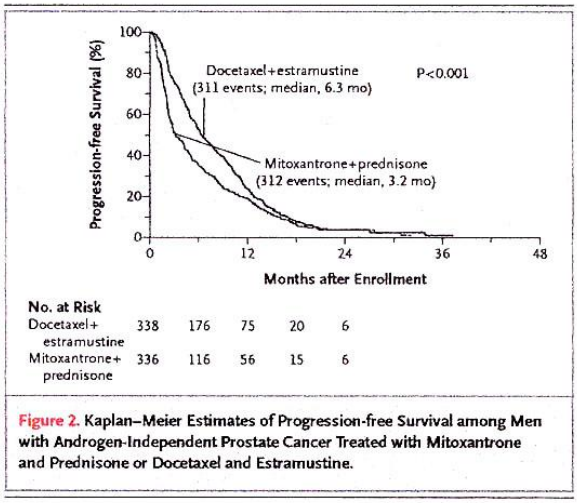

Figure 2. Kaplan–Meier Estimates of Progression-free Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

Figure 4

The "payment" for these benefits - the postponement of progression and death - is paid in the currency of toxicity. Figure 5 below highlights the incidence of various toxicities for the Tax-327 and SWOG trials. Petrylak, ibid, concluded "Treatment with estramustine and docetaxel moderately increases survival at a cost of an increased rate of adverse events", i.e., grade 3 and 4 neutropenic fevers, nausea and vomiting, and cardiovascular events - all significantly more frequent. In an article to be published in the May, 2005, JCO, "Prostate Cancer Chemotherapy: Emerging From the Shadows" Bruce Roth wrote: "However, comparison of data from the two definitive phase III trials would suggest that there is likely little, if any, survival benefit from the addition of estramustine to a docetaxel regimen.

A clear indication for chemotherapy is the desire to reduce tumor related pain, and this is achieved in all these regimens in 25% to 35% of instances, usually for a duration of 3 to 5 months. In the face of

Toxicity

SWOG 99-16	Docetaxel/Estramustine	Mitoxantrone/Prednisone	
• Neutropenia	12.5%	16%	P=0.22
• Neutropenic fever	5%	2%	P=0.01
• Cardiovascular	15%	7%	P=0.001
• Neurologic	7%	2%	P=0.001
• Infection	14%	7%	P=0.004
• Gastrointestinal	19%	4%	

TAX-327	Docetaxel – q 3 wks	Docetaxel – weekly	Mitoxanthrone
• Neutropenia	32%	2%	22%
• Neutropenic fever	3%	0%	2%
• Diarrhea	32%	34%	10%
• Neuropathy	30%	24%	7%
• Edema	19%	12%	1%
• Impaired LVEF	10%	8%	22%

The toxicity for no treatment in an asymptomatic patient is zero

Figure 5

objective metastateic disease the desire is to objectively reduce tumor volumes, but this occurs less frequently - in only about 10% to 17% of cases. If treatment effectiveness can be verified for agents with less or minimal toxicity - possible examples being "Atrasentan" (an endothelin A receptor inhibitor), or vaccines (i.e., Dendreon's "Provenge"), then the favorable relationship between benefit and toxicity will allow intervention earlier in the course of HRPC.

Dr. Tomasz Beer, Oregon Health & Science University, has piloted several trials to attempt to maximize benefits while reducing toxicity. His phase II study of weekly Docetaxel showed a median survival of 10+ months, a PSA response of 44%, a median TTP of ~ 5 months, a measurable disease response of ~ 31%, , and a 37% decrease in pain. A follow-up phase II study of weekly Docetaxel plus high-dose calcitriol produced a median survival of 19.5 months, a median TTP of 11.4 months, and an 81% > 50% PSA decline. The results of a randomized, double blinded comparison of these two regimens will be presented at the 2005 ASCO meeting.

The question of the optimal duration of chemotherapy is also under study. Dr. Eisenberger at Johns Hopkins has opted for a strategy of treatment until maximal response followed by a period of observation, and retreatment on relapse. And Dr. Beer reported his observation on this strategy in British J Cancer 91(8) 2004. Eight of 37 men had a treatment response to PSA < 4 ng/mL and these eight then had intermittent treatment: 11 months to maximal response followed by one or more treatment "holidays" of ~ 5 months each. The overall time from the start of therapy to treatment failure for these eight men was 26.5 months - and they experienced an associated benefit of an improved quality of life.

Bottom Line: An active exploration is underway to find the optimal chemotherapy agents and best strategy for their implementation in hormone refractory prostate cancer. The goal is achieveing increased benefit while minimizing toxicity. An understanding of the natural history of HRPC gives perspective for evaluating the results of new treatments.

DIAGNOSTICS: Phase III Trial Of Toremifene In High-Grade Prostatic Intraepithelial Now Open For Registration

Encouraging results of a Phase IIB trial comparing the selective > estrogen receptor modifier (SERM), toremifene (20 mg, po, qd), to a placebo reported a significant reduction of prostate cancer risk at one year (24.4% vs 31.2%) in a study of 514 men with HGPIN. A full discussion of this issue appeared in the PCa Commentary, January 2005 (An electronic archive copy can be found on the SPI website – seattleprostate.com / Physician Education / PCa Commentary / Diagnostics – "High Grade Prostatic Intraepithelial Neoplasia Is A Disease".) Dr. Lilly, urologist, Swedish Hospital, Seattle, is the local principal investigator for the now open phase III, randomized double-blind, placebo controlled trial sponsored by the GTX Corp., the maker of apodene" (toremifene). Eligibility requires that applicants have a biopsy within the prior 6 months negative for cancer and showing HGPIN. Concomitant atypia (ASAP) is permitted.The PSA level may not be higher than 12 ng/mL. During the 18 month study repeat biopsies will be done at 12 and 18 months. All pathology will be reviewed by Dr. Bostwick. For further information and registration contact Dr. Lilly his office phone, 206-292-6488, or email at jlilly@seattleurological.org.