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Current Perspective

When to start cytotoxic therapy in asymptomatic patients with hormone refractory prostate cancer?

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ABSTRACT

Until the publication of two pivotal trials, there were no treatment options available that did prolong the overall survival in men with hormone refractory prostate cancer (HRPC). Currently, docetaxel-based cytotoxic treatment is considered as a standard of care in all the patients with progressive metastatic HRPC. The use of this treatment regimen renders an equal survival benefit in all the subgroups of patients; however, there is a substantial difference in the overall survival between the subgroups. This review addresses the optimal timing of the cytotoxic treatment in asymptomatic patients with HRPC.

1. Introduction

The initial treatment in patients with advanced prostate cancer is androgen deprivation. Although the majority of patients show a good clinical response after initiation of hormonal therapy, hormone independent disease will develop after an average period of 18 months. The mechanisms of the development of hormone resistance are largely unknown, although the molecular changes of the androgen receptor, e.g. mutation or amplification can explain some of the cases. Until recently, there was no proven therapy to improve the survival in patients with prostate cancer that had become refractory to hormonal manipulations. Following the publication of the two pivotal trials (TAX327 and SWOG 99-16) in 2004, docetaxel-based chemotherapy became a standard treatment in men with hormone refractory prostate cancer (HRPC).[1,2] Both trials enrolled the whole spectrum of patients with progressive metastatic HRPC previously untreated with cytotoxic therapy, including patients with PSA progression only, bone-scan progression, as well as widespread symptomatic disease progression.

At inclusion in the TAX327 about 21% had a rising PSA as sole evidence of metastatic disease progression and 55% were free of pain, whilst in the SWOG 99-16, 19% had progressive HRPC based on PSA progression only, and 64% of patients were free of bone pain or bone pain was mild and not interfering with function.[1–3] Forest-plot analysis indicated that the survival benefit in the subgroups analysed, including symp-

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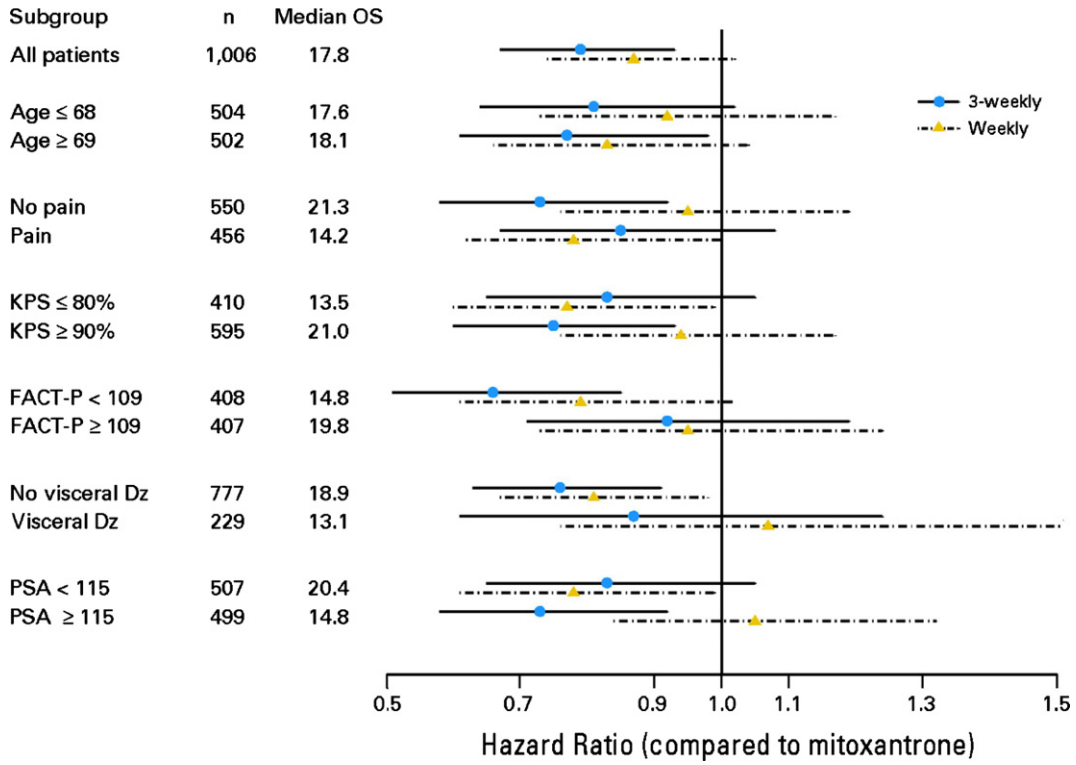

Fig. 1 – Forest-plot analysis of the various subgroups treated on the TAX327 trial. At left are the subgroups defined, the number of patients per subgroup and their median survival time independent of treatment. At right is a forest plot showing the median hazard ratio and their 95% confidence intervals (CIs) for survival on the docetaxel arms compared with the mitoxantrone arm. OS: overall survival, KPS: Karnofsky performance status, FACT-P functional assessment of cancer therapy-prostate, Dz: disease, PSA: prostate-specific antigen. Reprinted from Armstrong et al.[3] with permission from the American Association for Cancer Research.

tomatic versus asymptomatic disease, was identical (Fig. 1).[4] Therefore, it remains open to debate whether all the patients with metastatic HRPC should immediately start with docetaxel therapy when progression is recognised, or that a group can be identified for whom rapid disease progression and death is less imminent.

This review addresses the question if such a distinction can be made between a group of patients in whom the initiation of cytotoxic treatment can be delayed without adverse sequelae and a group that is best served with immediate start of cytotoxic treatment.

2. Current cytotoxic treatment in patients with HRPC

Docetaxel has been proven the first and up till now only cytotoxic therapy that improves the overall survival in men with HRPC. This benefit has been demonstrated in two large randomised trials: TAX327 and SWOG 99-16, both designed to test for survival improvement of a docetaxel-based schedule compared to mitoxantrone (12 mg/m^2 every 3 weeks) combined with 5 mg prednisone twice daily (MP).[1,2] In the TAX327 study (n = 1006), the comparator arm of MP was tested against docetaxel administered every 3 weeks at a dose of 75 mg/m^2 (DP3w) or weekly at a dose of 30 mg/m^2 (DP1w) plus the same prednisone regimen. The hazard rate (HR) for death was the lowest in patients treated with DP3w (HR 0.74, p = 0.009).[1] The initial analysis showed a survival improvement in patients treated with DP3w from 16.5 months to 18.9 months.[1,2] In a recent survival update with 85% events, the survival advantage of DP3w has slightly increased to 2.9 months (p = 0.004).[4]

The SWOG 99-16 study randomised 674 eligible patients to receive MP or estramustine (three times daily 280 mg on days 1–5) and docetaxel 60 mg/m^2 (ED) and confirmed the benefit of a docetaxel-based regimen, with a significant improvement in OS from 15.6 months to 17.5 months.[2]

Due to crossover between the treatment arms after disease progression in a substantial segment of the patients in both trials (especially due to the docetaxel treatment in the later course of disease in those patients initially treated with MP), the survival benefit of the docetaxel-based regimen is likely underestimated as compared to MP.[1,2,4]

3. Adverse events by docetaxel in patients with HRPC

In general, DP3w is well tolerated in patients with HRPC. In more detail, grades 3 and 4 neutropenia in the TAX327 trial was encountered more frequently in the DP3w-treated patients as compared to the patients treated with DP1w or MP (32%, 2%, 22%, respectively). Yet, the incidence of febrile

neutropenia was low in all the groups (3%, 0%, 2%, respectively).[1]

Grade 3 or 4 non-haematological toxicity was uncommon in all the treatment arms of TAX327.[1] However, the addition of estramustine to docetaxel in SWOG 99-16 resulted in 19% grades 3 and 4 nausea and vomiting and 13% cardiovascular events (mainly deep venous thrombosis and pulmonary embolism) as compared to 6% of both toxicities in the MP group. Five deaths in the TAX327 were probably related to treatment: three in the mitoxantrone group and one in each docetaxel group,[1] whereas 12 treatment-attributable deaths occurred in the SWOG 99-16: 8 in the ED group and 4 in the MP group.[2]

Although only available by indirect comparison, based on a more favourable toxicity pattern by using DP3w as compared to ED and the absence of a difference in the survival benefit between these two treatment regimens, DP3w has become the international standard treatment of patients with progressive metastatic HRPC.

4. Predictive factors for survival: the TAX 327-based nomogram

In TAX327, median survival times were calculated for distinct subgroups as a function of the treatment arm. It is important to notice that the survival benefit is equal for the patients with and without pain on the entry of the study, patients with baseline PSA equal or above the median value of 115 ng/ml versus below this level and in older as well as in younger patients. Although the benefit is similar, there is a substantial difference in the overall survival (OS) in the patients with and without pain (14.4 and 21.3 months, respectively) (Fig. 1).[4]. Apparently, once symptoms occur, further disease progression and subsequent death become more imminent. By realising that in some subgroups the urgency to initiate the cytotoxic therapy is higher or lower than average, further attempts were made by trying to identify the predictive factors. Given the fact that the baseline PSA has a substantial predictive potential for OS (high versus low baseline PSA

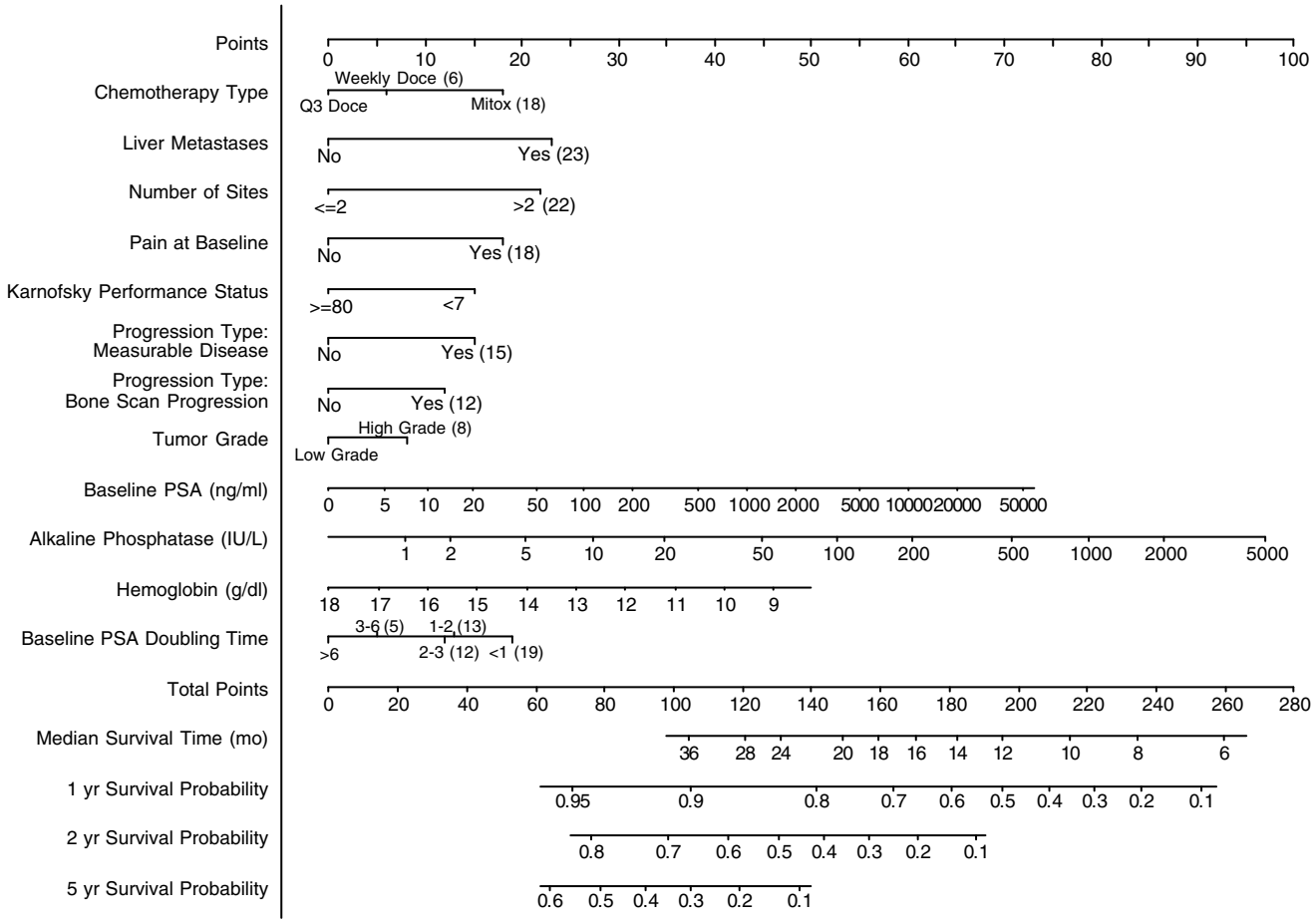

Fig. 2 – Nomogram for survival of patients with progressive HRPC. Instructions for physician: Locate the liver metastasis axis. Draw a straight line upward to the points axis to determine how many points towards survival the patient receives for the presence or absence of liver metastases. Repeat this process for each predictor variable and sum the points for each predictor. Locate this sum on the total points axis. Draw a straight line downward from the total points axis to identify the predicted median survival and the predicted 1-year, 2-year and 5-year overall survival probabilities. Reprinted from Berthold et al.[4] with permission from the American Society of Clinical Oncology.

14.8 and 20.4 months, respectively)[4], PSA kinetics were included in univariate and multivariate analysis.[3] After the identification of significant predictive factors, described in the following paragraphs, the TAX327-based nomogram was constructed (Fig. 2).[3]

In a subset analysis of the TAX327, comprising all the patients with 3 or more baseline PSA measurements, the value of baseline PSA as well as baseline PSA doubling time (PSA-DT) was studied.[3] In a univariate analysis, PSA-DT showed to predict an increased risk of death (HR 1.46) if the value was below the median PSA-DT of the whole group (55 days). In the multivariate analysis, the HR is lowered from 1.46 to 1.19 but still shows an important trend ($p = 0.066$). In a bivariate analysis using baseline PSA and PSA-DT, PSA-DT showed to be of additional value in addition to baseline PSA-values. Oudard et al., studying 250 patients, previously reported the relevance of the speed of PSA-DT before the onset of cytotoxic therapy. The median PSA-DT at the time of initiation of chemotherapy in that cohort was 45 days, and by using the median as cut point the median survival was significantly shorter in patients with a PSA-DT below 45 days compared to those with a slow PSA-DT (16.5 versus 26.4 months, $p = 0.04$). In a multivariate analysis, the HR for risk of death was estimated to be 1.39 ($p = 0.03$); however, a bivariate analysis (of PSA-DT and baseline PSA) assessing the additional information gained by using PSA-DT on top of baseline PSA is not given.[5] In the TAX327-based nomogram, a further refinement of PSA-DT has been made by using month-groupings (<1 month, 1–2 months, 2–3 months, 3–6 months, >6 months) based on a significant trend of reduced risk if PSA-DT is longer.

Haemoglobin and alkaline phosphatase are classical prognostic factors of survival in untreated patients with HRPC.[6] In the construction of the predictive model by Armstrong, they also appeared to be useful significant predictors of survival with HR of 1.11 and 1.27, respectively.[3]

Furthermore, two additional factors became apparent to be of predictive value, the first being the type of progression at baseline: bone scan progression, progression based on measurable disease or PSA-only progression as a single sign of progressive metastatic disease. Whilst the first two groups are associated with an increased risk of death (HR 1.36 and 1.26, respectively), the latter is associated with a more favourable outcome (HR 0.75). Interestingly, also the occurrence of 2 or more new hot spots on a bone scan, even in the absence of symptoms, had independent prognostic importance for survival ($p = 0.01$). Pain at study entry emerged to be of predictive value as well, by negatively influencing the overall survival (HR 1.48) in the multivariate analysis.[3]

In the analysis resulting in the TAX327-based predictive nomogram several other factors also emerged as relevant factors in predicting survival: the presence of liver metastases, number of metastatic sites (>2 versus $\leqslant$2), performance status (Karnofski index $\geqslant$80 versus $\leqslant$70), tumour grade (Gleason $\geqslant$8 versus $\leqslant$7) (HR 1.66, 1.63, 1.39 and 1.18, respectively).[3]

All the aforementioned factors are incorporated in the TAX327-based nomogram by assigning points in accordance to their relative importance in predicting the survival after DP3w. Counting up these points results in a score that leads to an estimate of median survival time as well as a 1-year, 2-year and 5-year survival probability.[3]

5. The nomogram in perspective

HRPC is a heterogeneous entity with rather well-characterised factors associated with outcome. Combining these factors allowed the assemblance of a prognostic model based on 1101 patients treated within the context of 6 Cancer and Leukemia Group B studies.[6] The factors used in this nomogram to estimate 12- and 24-month survival probability and median survival time were the presence or absence of visceral disease, Gleason score, performance status, baseline PSA, lactate dehydrogenase, alkaline phosphatase and haemoglobin.[6]

In contrast to the Halabi nomogram, which is regarded as a prognostic nomogram, the TAX327 nomogram can be seen as a predictive nomogram for men with HRPC treated with cytotoxic therapy, because in the population used for the Halabi nomogram only 19% of the patients were treated with cytotoxic treatment, whilst the TAX327 population consisted entirely of patients treated with cytotoxic therapy. Factors derived from the studies using an agent (e.g. docetaxel) that has proven to prolong survival, can be seen as predictive factors, giving rise to the construction of a tool that can be used to inform the patients on the effect of that specific therapy. Although the external validation of this newly developed nomogram still remains to be done, it will be of great help informing patients and it may provide an important tool to determine the potential benefit for an individual patient with HRPC.

6. How to use the nomogram in clinical practise?

Although it is currently known that asymptomatic patients have a better OS, there are no data available what the consequences are of delaying the initiation of cytotoxic therapy in these patients. Patients with HRPC may remain asymptomatic for a prolonged period of time without intervention, whilst others only have an asymptomatic time frame of no more than weeks or months. Delaying cytotoxic therapy may be justified in the first subgroup, but one can postulate that in the latter group with a survival probability of one year or less, the initiation of docetaxel-based treatment should not be delayed. Being asymptomatic without cytotoxic therapy must be well weighed against extended freedom of disease progression by the cytotoxic therapy.

Resolving the aforementioned dilemma could be done by performing a study using docetaxel-based treatment in asymptomatic HRPC and randomise patients between immediate treatment versus treatment initiated if symptoms become apparent. However, chances that such kind of trial will be done are low and without the results of such kind of study, guidance could be found, by weighing the factors by using the predictive TAX327-based nomogram. The strength of the nomogram will increase if it is validated in another data set, for example the population studied in the SWOG 99-16.

In our opinion and based on the data summarised in the nomogram, in patients with HRPC with a PSA-only progression as single sign of metastatic disease with a low baseline PSA and a slow PSA-DT, a normal or slightly raised alkaline phosphatase and normal or slightly lowered haemoglobin delaying the introduction of cytotoxic therapy by means of

docetaxel is a valid option. In contrast, in those asymptomatic patients for whom the development of further disease progression is more imminent (based on high PSA-DT and/or high baseline PSA and/or bone scan progression and/or visceral progression), the initiation of cytotoxic therapy should not be delayed.

Conflict of interest statement

None declared.

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