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RESEARCH ARTICLE

Castration-Synchronized Upfront Docetaxel for metastatic Hormone Sensitive Prostate Cancer considering Epithelial to Mesenchymal Transition

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ABSTRACT

Upfront docetaxel therapy for metastatic hormone sensitive prostate cancer (mHSPC) has been reported to be improved outcome, although the best timing to start decetaxel and/or the duration of chemotherapy have not been cleared. We consider epithelial to mesenchymal transition (EMT) at the beginning of the hormonal therapy would be the mechanism to obtain apoptosis tolerance of prostatic cells. For localized prostate cancer, we used LH-RH antagonist (degarelix) twice and performed high-intensity focused ultrasound therapy (HIFU) after two weeks of the first degarelix, the timing of inducing EMT. This regimen apparently improved HIFU results. So for mHSPC, we started two to three courses of upfront docetaxel synchronously the beginning of the androgen deprivation therapy (ADT). Of 38 mHSPC patients underwent upfront docetaxel with our protocol, 18 patients maintained low prostate specific antigen value less than 0.1 ng/ml for more than two years without adding new androgen axis targeted therapy agents (ARAT). Although recent study suggests all mHSPC patients should receive systemic triple therapy including ADT, docetaxel and ARAT, our study indicated that upfront docetaxel use considering EMT may select the patients requiring triple therapy, and reduce a burden both for the patients and medical economy.

Keywords: Prostate Cancer, hormone-sensitive, Epithelial to mesenchymal transition, upfront docetaxel

Introduction

Upfront Docetaxel therapy for metastatic hormone sensitive prostate cancer (mHSPC) has been reported to be improved outcome by some studies such as the GETUG-AFU-15,[1] CHAARTED,[2] and STAMPEDE NCT00268476.[3] Following these studies, upfront docetaxel therapy is becoming a standard care for patients with mHSPC.[4] In PEACE 1 study, patients treated with upfront docetaxel is assigned to both control arm and new treatment arm.[5] However, the best timing to start docetaxel and/or the duration of upfront chemotherapy have not been cleared.[6] Eigl *et al*. reported an *in vivo* synergistic effect of taxanes and androgen deprivation therapy (ADT).[7] They found that homogenous hormone-sensitive tumor engrafted mice receiving one time paclitaxel and simultaneous castration, exhibited a delayed median time to progression compared to those treated with sequential ADT and two courses of chemotherapy. They concluded that "Timing is everything: simultaneous rather than sequential chemo-hormonal therapy is more effective for prostate cancer."

In this review, we present a new high intensity focused ultrasound (HIFU) therapy combined with short course hormonal therapy for early stage prostate cancer considering the mechanism of apoptosis tolerance. Then according to the improved HIFU results, we applied the concept to upfront docetaxel use for mHSPC patients, and discuss the appropriate timing and duration of upfront docetaxel to obtain a better outcome.

Epithelial to Mesenchymal Transition is supposed mechanism of apoptosis tolerance

Akakura and Bruhovsky *et al*. reported the reason why ADT for prostate cancer treatment must continue eternally. They supposed that small numbers of cancer cells obtain apoptosis tolerance at the beginning of the ADT, and keep alive at cell arrest phase as long as ADT continues, while most of the hormone-sensitive cancer cells go into apoptosis.[8] In that report, the apoptosis tolerance would be obtained around two weeks after castration. If some kind of definitive therapy added to this period, complete cure by "total cell kill" might be possible.

Sun *et al*. for the first time reported that androgen deprivation induces epithelial to mesenchymal transition (EMT) in both normal prostatic cells and prostate cancer.[9] Li *et al*. reviewed that EMT and cancer stem cells play crucial roles during the development of castration resistance of prostate cancer. Castration can induce EMT that may enhance the stemness of cancer stem cells, and produce castration-resistance and metastasis. Furthermore, reverse of EMT may attenuate the function of cancer stem cells and may inhibit castration-resistance and metastasis.[10] Three weeks administration of chlormadinone acetate (synthetic progesterone) (CMA) proved to induce stem cell transformation of prostatic cells by basal cell proliferation (Figure 1).[11] The proposed mechanism of this phenomena is indicated in Figure 2.[12]

Figure 1. Basal cell proliferation and stem cell transformation observed after three weeks administration of CMA. Control specimen without CMA stained with HE (a), and CD44 (stem cell marker) (b). Specimen with CMA HE (c), and CD44 (d), reduced from 10x.

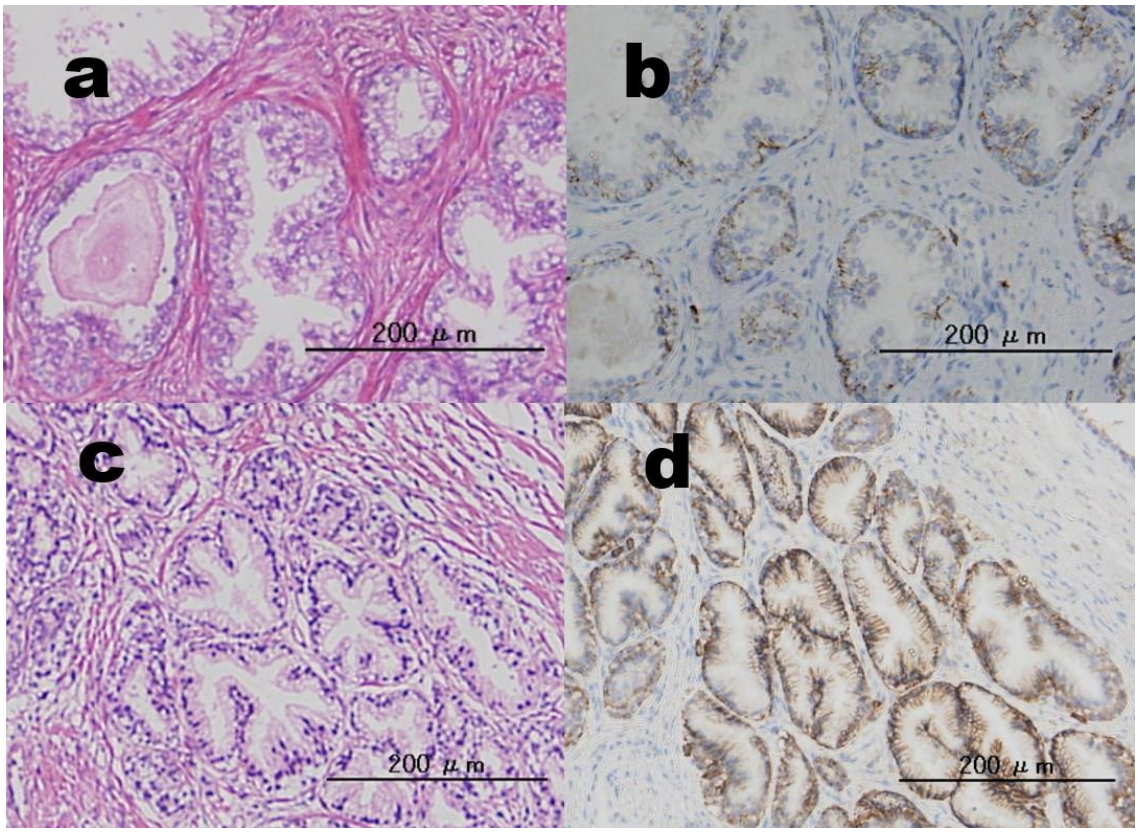
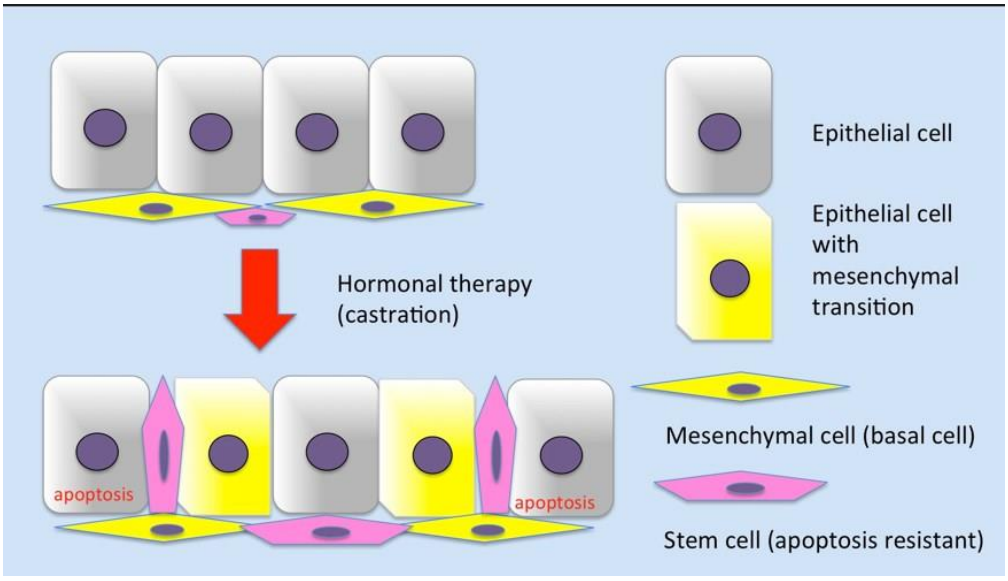


Figure 2. Proposed schema of EMT induced by hormonal therapy. Apoptosis-resistant stem cells among mesenchymal basal cells, proliferate into apoptotic-luminal cells and act as intermediate cells representing transition state.



Jaworska and Szliszka reported that cancer cells re-sensitized to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by docetaxel when cancer stem cells reduce TRAIL function for PC3 prostate cancer cells.[13] Zhu *et al*. reported tubulin-targeting chemotherapy using docetaxel regulate androgen mediate signaling by prevention of nuclear accumulation of androgen receptors.[14] Martin *et al*. reviewed tubulin targeting chemotherapy inhibit cancer cells to obtain metastatic function including EMT.[15] These results suggest docetaxel can effectively inhibit transformation of cancer cells into apoptosis tolerance mediated by EMT.

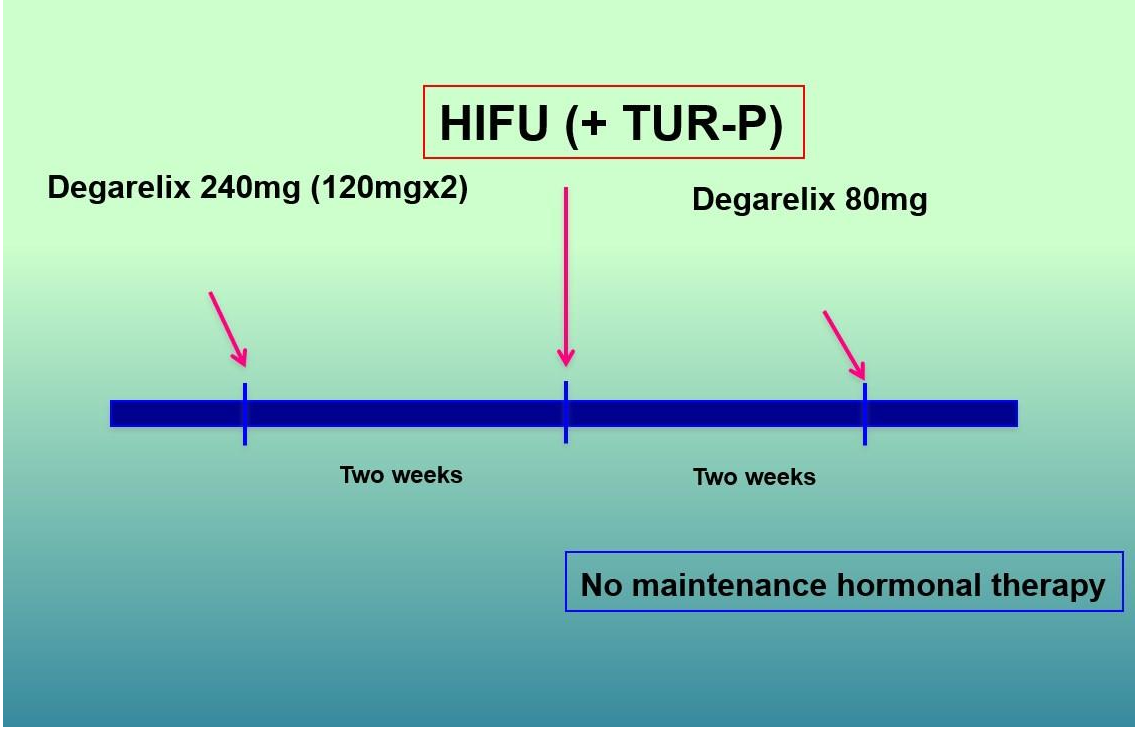
Whole grand HIFU with Short Course Degarelix

Although HIFU therapy has been used as less-invasive treatment for early stage prostate cancer, it is not sited as standard therapy in any guidelines in the world, presumably because the results are not as effective as surgery or radiation therapy.[16] Previous treatment results in our hospital on HIFU mono-therapy indicated, although about 60% of patients, whose post-HIFU prostate specific antigen (PSA) level maintained below 1 ng/ml, showed excellent results, among the half of the patients, whose post-HIFU PSA value rose again after decreased below 1 ng/ml, or whose post-HIFU PSA value remained three or four ng/ml, had worse prognostic results, such as cancer positive by post-HIFU prostate biopsy.

Methods

Following Akakura and Bruhovsky theory, we tried new HIFU treatment regimen showing as follows, degarelix (LH-RH antagonist) 120 mg × 2 subcutaneous injection, HIFU + transurethral resection of prostate (TUR-P) two weeks after the first degarelix use under general anesthesia, degarelix 80 mg subcutaneous injection two weeks after HIFU, no maintenance hormonal therapy thereafter (only twice) (Figure 3).[17]

Figure 3. Schema of whole grand HIFU with short course degarelix

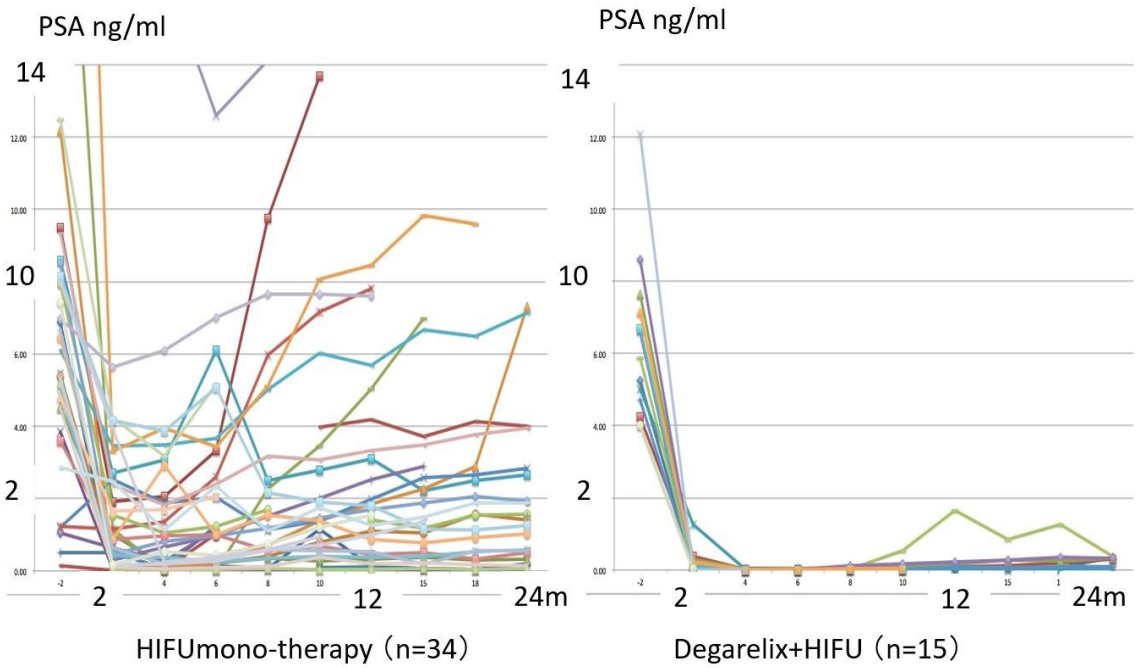


We use degarelix as medical castration, because it can reduce androgen to castrate level as early as surgical castration, and supposed to induce massive prostatic cellular apoptosis within two weeks.[18] The definitive additional local treatment with HIFU can be made two weeks after the first hormonal therapy to obtain "total cell kill". The clinical courses by PSA values of 15 HIFU + degarelix therapy were compared with previous 34 HIFU monotherapy patients. The mean PSA values between HIFU monotherapy and HIFU + degarelix therapy were statistically evaluated with Mann-Whitney's U test at each clinical course point, as non-parametric values between these groups.

Results

The mean and standard error of pretreatment PSA level of the 34 patients underwent HIFU monotherapy and 15 patients underwent HIFU + degarelix were 10.57 ± 2.16 ng/ml and 6.15 ± 0.60 ng/ml respectively ($p=0.22$). The mean PSA values 4 months post HIFU were 1.74 ± 0.49 ng/ml and 0.01 ± 0.00 ng/ml ($p<0.01$). The mean PSA values 12 months post HIFU were 2.57 ± 0.68 ng/ml and 0.08 ± 0.04 ng/ml ($p<0.01$). The mean PSA values 24 months post HIFU was 2.72 ± 0.85 ng/ml and 0.14 ± 0.04 ng/ml ($p<0.01$). (Figure 4).

Figure 4. Clinical courses by PSA values of all patients with HIFU mono-therapy (left), and short course degarelix + HIFU (right).



This concept is totally different from external radiation therapy with two years adjuvant hormonal therapy for high risk localized prostate cancer, in that we use thermal damage to whole prostatic gland with HIFU in order to inhibit EMT to obtain apoptosis tolerance. Of course, HIFU monotherapy may obtain complete cure, however for the sake of completeness, apoptosis of 99% of prostatic cells by the two-time degarelix are added.

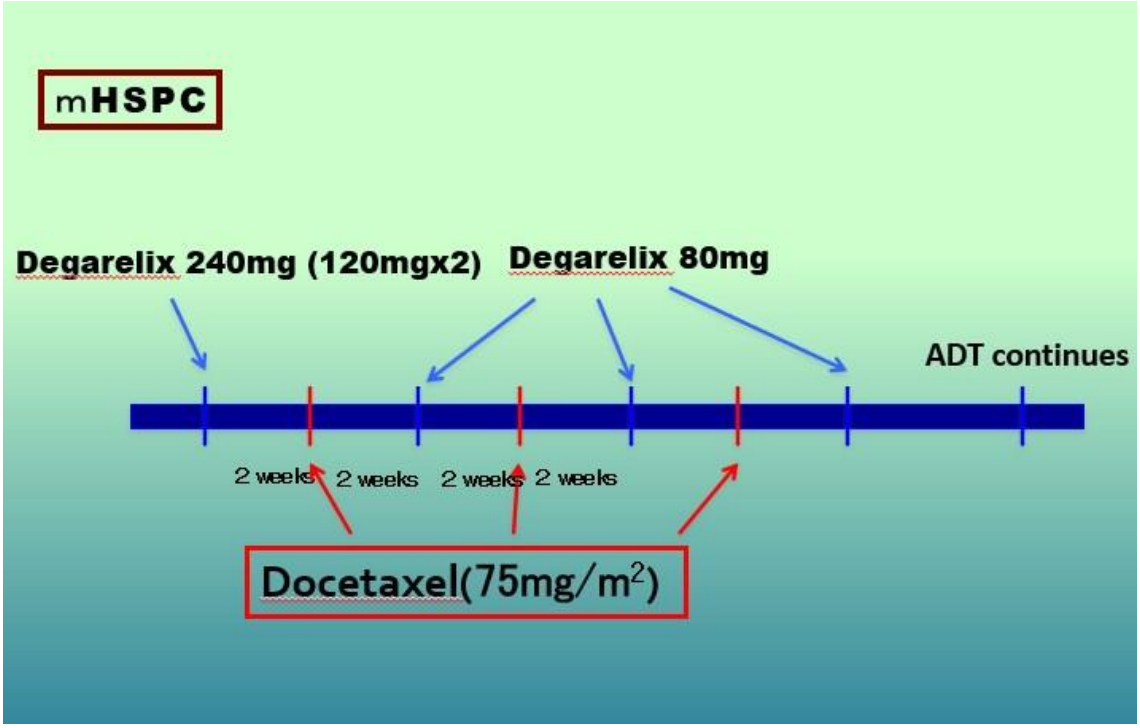
Castration synchronized upfront docetaxel for mHSPC

As we confirmed an effectiveness of the proposed concept in localized prostate cancer, we tried to use two to three courses of docetaxel for the purpose of inhibiting EMT at the beginning of ADT to advanced metastatic hormone sensitive prostate cancer.

Methods

Precise methods were shown in previously published report.[19] In short, of 41 stage IV new prostate cancer patients during the period of Oct. 2014 to Aug. 2020, treated with upfront docetaxel and degarelix, 38 patients who could be followed more than 24 months (mean 45.0 months) were analyzed. Patients who had been treated surgically or radiologically as localized prostate cancer and advanced thereafter were excluded, because mostly they had already been hormonally treated at the time of PSA recurrence. No age limitation was provided if the patient could approve chemotherapy. Docetaxel was used two to three courses monthly basically 75 mg/m^2 dose starting two weeks after the induction of the first degarelix (Figure 5).

Figure 5. Schema of castration synchronized upfront docetaxel for mHSPC.

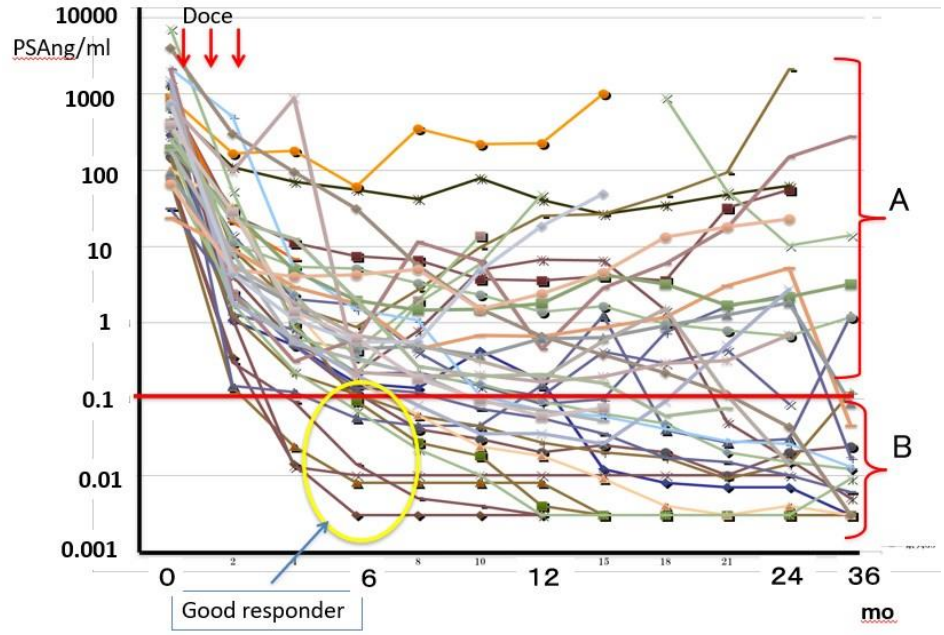


As this study was not a controlled study but an observational study, for the patients underwent upfront docetaxel and degarelix, attending physician added other drugs and therapies afterwards according to necessity, such as regional irradiation, abiraterone, enzalutamide and cabazitaxel. Patients, whose initial chief complaint were progressive limb paralysis due to vertebral metastasis, underwent irradiation for the metastatic site and degarelix as a first therapy. The PSA values between group A and B were examined with Mann-Whitney's U test at each clinical course point.

Results

The clinical course of this therapy was divided clearly into two groups according to PSA values. Of 38 patients, 20 patient's PSA did not decrease below 0.1 ng/ml around 6 months and gradually rose afterwards. These patients were categorized as group A. PSA in another 18 patients decreased below 0.1 around 6 months and kept low level during the follow up period. These patients were categorized as group B (Figure 6a).

Figure 6a. Clinical course by PSA values of all patients are indicated in Semi-log plot. Patients whose PSA did not decrease below 0.1 ng/ml around 6 months are categorized as group A, and the others as group B. Doce: docetaxel, mo: months



Although statistically not significant, the initial group A's PSA were higher than group B's (average 1,058 and 580 ng/ml), however, number of metastases, pathological grade group, and bone metastatic extent of disease (EOD) showed no difference between them (Table).

Table. Patients and clinical profiles

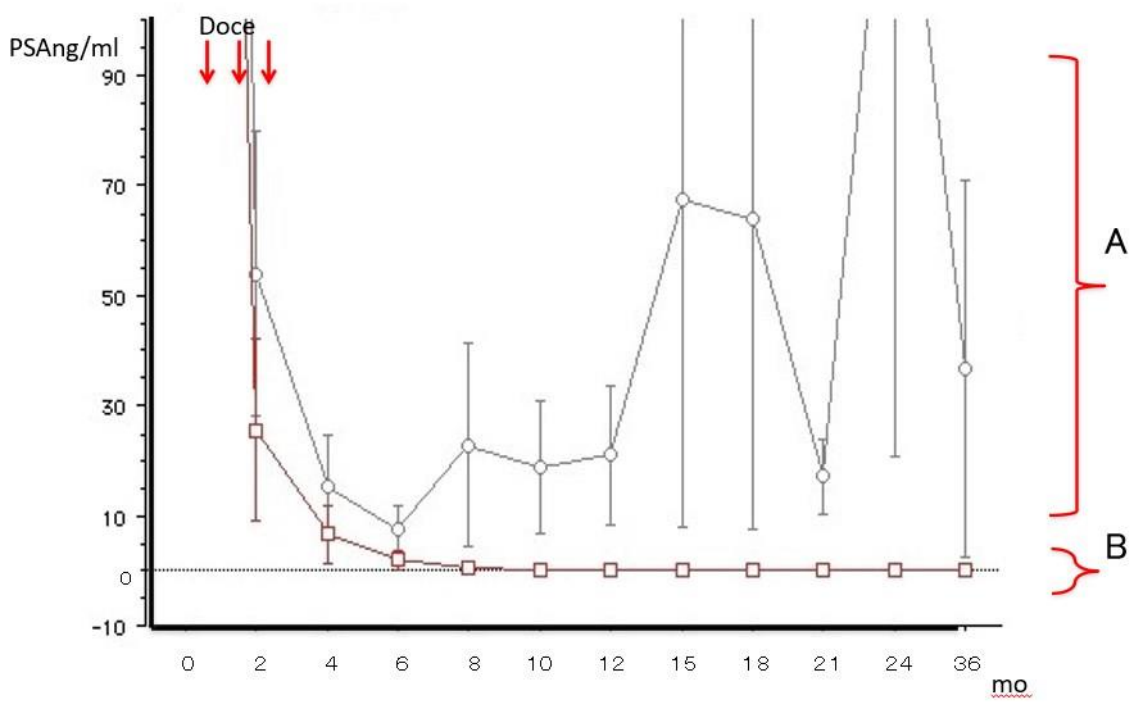
		A	B
No of cases		20	18
Age		71.0 (50-83)	68.1 (52-77)
Initial PSA(ng/ml)		1058.5 (23-7184)	580.0 (31-4017)
Cancer death		5	0
Grade Group	3	4	1
	4	8	8
	5	8	8
EOD	1 - 2	3	8
	3 - 4	12	7

Age average (minimum-maximum), Initial PSA values average (minimum-maximum)

Pathological grade group: Gleason sum ≦6 →1, 3+4 → 2, 4+3 → 3, 8 → 4, 9 or 10 → 5. EOD: extent of disease.

Though group A patients had various additional therapy after PSA failure by physician's decision, eleven out of 18 group B patients only underwent hormonal and upfront docetaxel therapy. Other 7 group B patients underwent irradiation therapy for bone metastasis. Five cancer deaths were recorded during the follow up period in group A. No cancer death was observed in group B. PSA values of group B were statistically lower than group A all through after 4 months of clinical course ($p<0.01$) (Figure 6b).

Figure 6b. Clinical course by PSA values of group average ± SE ng/ml in lineal plot.



Discussion

In recent years, upfront use of docetaxel for mHSPC showed significant retardation of the development to hormone-refractory state.[20] As a hormonal agent, LHRH agonist was mainly used in previous studies. Furthermore, the timing to start upfront chemotherapy varied from simultaneous to several months from the beginning of hormonal therapy according to the study design.

At first, we considered the mechanism and timing of apoptosis tolerance induced by EMT and examined the concept using short term degarelix and HIFU for early stage prostate cancer. Then confirming the improved HIFU therapy outcome using this concept, we tried upfront docetaxel for mHSPC in relatively short courses than previously reported studies.[21] As a result, about a half of our enrolled mHSPC patients could be managed only with upfront docetaxel and ADT for more than two years. Our results may be a clinical confirmation of previous Eigl's concept by animal study.[7]

The mechanism and timing of development of castration resistance are still debatable. Two models were proposed such as; "adaptation emergence" and "clonal selection".[22] The former model suggested that prostate cancer is composed

of homogenous hormone dependent cells, and castration resistance emerges through genetic/epigenetic conversion of cells from androgen-dependent to independent status. Whereas the latter model indicates that prostate cancer is composed of heterogenous major hormone dependent and minor hormone independent cells. Under an androgen-deprived environment, the castration-resistant cells are selected for survival and obtain proliferative advantage, and finally all cells composed of hormone independent. Especially to the former adaptation emergence process, the contribution of EMT has been proved in the several basic studies.[9] And for the purpose of inhibiting EMT and/or mutation of androgen receptor, microtubule-targeting agents; docetaxel is reported effective.[13,15] We consider from our results that docetaxel should be used at the timing of the first hormonal use, that is the timing of adaptation emergence to acquire apoptotic tolerance for hormonal therapy.[10]

Our results suggested that in group A, small numbers of survived castration resistant prostate cancer, those existed at the first visit, continued proliferation after the chemotherapy as a "clonal selection". Whereas in group B, especially in patients applying no other treatment modality other than ADT and docetaxel, upfront docetaxel prevented EMT to obtain "adaptation emergence", and induced total cell kill. Second prostate biopsy for two patients, whose PSA value below 0.1 ng/ml for more than two years and quitted ADT, indicated no residual cancer on specimens. This result may prove our total cell kill theory.[19] However, these two patients showed small rise of PSA about one year after quitting ADT (0.2 to 0.4 ng/ml, no published data). So, ADT was restarted for these two patients. PSA values of these patients reduced below 0.1ng/ml thereafter, suggesting very small numbers of hormone-sensitive benign and/or malignant cells, though localization was not clear, remained alive.

As we mentioned, the duration of upfront docetaxel of previously reported studies were six to nine courses. To complete these courses for all mHSPC patients as a standard therapy compel fairly physical exhaustion. We consider two or three courses of upfront docetaxel followed by ADT would be not a painful treatment for all patients.

Recent studies suggested all mHSPC patients should receive systemic triple therapy including ADT, docetaxel and new androgen receptor-axis-targeted therapy (ARAT).[23] However, new ARAT agents are expensive and they must be continued for many years as long as they are effective. Our study suggested about a half of mHSPC patients could be managed without new ARAT. If all mHSPC patients have destined to use upfront docetaxel as a standard therapy, castration synchronized upfront docetaxel may eliminate unnecessary patients for triple therapy. The decision to add costly ARAT can be made at the timing of six months after starting ADT and docetaxel, and if PSA decrease below 0.1ng/ml, only ADT should be continued. We are certain that this decision making process is beneficial for both patients and healthcare providers.

Conclusion

Upfront docetaxel as a standard therapy for mHSPC should be used synchronously at the beginning of hormonal therapy, considering EMT that enables apoptosis tolerance to hormone-sensitive cancer cells. About a half of mHSPC patients could be managed without adding costly

new ARAT agents. This concept could select the patients requiring triple therapy.

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