Therapies for castration-resistant prostate cancer in a new era: The indication of vintage hormonal therapy, chemotherapy and the new medicines

doi: 10.1111/iju.13372

INTERNATIONAL JOURNAL OF UROLOGY

Therapies for CRPC on new era: The indication of vintage hormonal therapy, chemotherapy, and the new medicines

Journal:	*International Journal of Urology*
Manuscript ID	IJU-01275-2016.R2
Manuscript Type:	Review Article
Date Submitted by the Author:	n/a
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Key Words:	CRPC, New hormonal therapy, radium-223, vintage hormonal therapy, chemotherapy
Abstract:	When advanced prostate cancer recurred during hormonal therapy and became the castration-resistant prostate cancer (CRPC), "vintage hormonal therapy" such as antiandrogen alternating therapy or estrogen-related hormonal therapy was widely conducted in Japan until 2013. This vintage hormonal therapy controlled the progression of CRPC. When CRPC relapses during these therapies, chemotherapy using docetaxel has been conducted subsequently. Since new hormonal therapies using abiraterone acetate and enzalutamide which improve the prognosis of CRPC have been available in Japan from 2014, therapeutic options for CRPC increased. Moreover, the improvement of the further prognosis is promising by using cabazitaxel for docetaxel-resistant CRPC and radium-223 for CRPC with bone metastasis. Increase in therapeutic options gives rise to many questions including best timing to use them and the indication. Furthermore, physicians have to consider the treatment for the recurrence after having conducted chemotherapy. We want to argue the difference in hormonal therapy between Japan and western countries and problems when conducting new treatments, and importance of image in this review article.

Therapies for CRPC on new era: The indication of vintage hormonal therapy, chemotherapy, and the new medicines

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Abstract

When advanced prostate cancer recurred during hormonal therapy and became the castration-resistant prostate cancer (CRPC), “vintage hormonal therapy” such as antiandrogen alternating therapy or estrogen-related hormonal therapy was widely conducted in Japan until 2013. This vintage hormonal therapy controlled the progression of CRPC. When CRPC relapses during these therapies, chemotherapy using docetaxel has been conducted subsequently. Since new hormonal therapies using abiraterone acetate and enzalutamide which improve the prognosis of CRPC have been available in Japan from 2014, therapeutic options for CRPC increased. Moreover, the improvement of the further prognosis

is promising by using cabazitaxel for docetaxel-resistant CRPC and radium-223 for CRPC with bone metastasis. Increase in therapeutic options gives rise to many questions including best timing to use them and the indication. Furthermore, physicians have to consider the treatment for the recurrence after having conducted chemotherapy. We want to argue the difference in hormonal therapy between Japan and western countries and problems when conducting new treatments, and importance of image in this review article.

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Introduction

The initial treatment for advanced prostate cancer is mainly hormonal therapy. However, the treatment strategy is different between Japan and in western countries. Many physicians in western countries do not recommend combined androgen blockade (CAB) i.e., the combined use of castration and an antiandrogen [1]. Although addition of antiandrogen to castration for advanced prostate cancer may produce improvement of about 2% or 3% in overall survival, it does not produce great benefit for patients [2]. This may be one of the reasons why they prefer castration only. In contrast, advanced prostate cancer is treated with CAB at many institutions in Japan. At least until the first half of 2014, various forms of hormonal therapy (so-called vintage hormonal therapy) have been performed on cases of prostate cancer that have advanced to castration-resistant prostate cancer (CRPC) [3-5]. Dexamethasone also has favorable effects on CRPC [6]. Chemotherapy using docetaxel has become available for recurrence after these vintage hormonal therapies in Japan since 2008 [7]. And best supportive care (BSC) has been chosen once efficacy of docetaxel is lost.

Since 2014, novel drugs for hormonal therapy (enzalutamide and abiraterone) and chemotherapy (cabazitaxel) have been added to the coverage of the national health insurance

system in Japan, and therapeutic approaches to CRPC have changed. Radium-223, a therapeutic agent for bone metastases of CRPC, has also been made available for clinical use in 2016.

It is sometime difficult to choose vintage hormonal therapy and new drugs for CRPC. We argue the difference in management of hormonal therapies between Japan and in western countries and how to use new drugs in this review article.

Vintage hormonal therapy

The usefulness of CAB for advanced prostate cancer has been demonstrated for stage C and D1 cases in a prospective clinical study conducted in Japan, except D2 case [8]. In reality, however, there are many institutions in Japan that use CAB. CAB has been proven useful also for stage D2 cases through an analysis using the J-CaP database, although it was a retrospective study [9]. A possible reason why CAB is not very useful in western countries is that a lower bicalutamide dose of 50 mg/day is used in western countries, while the dose in Japan is 80 mg/day. It was clear that the higher dose of bicalutamide (100 mg/day or 150 mg/day) was more effective [10]. Therefore, it is potentially insufficient for 50 mg/day bicalutamide to exert the adequate antiandrogen effect. For CRPC occurring after CAB, it

was common in Japan to confirm the antiandrogen withdrawal effect [11] or perform alternative antiandrogen therapy [3]. In particular, it has been shown that alternative antiandrogen therapy decreased prostate specific antigen (PSA) in 60–80% of patients, and that decreased PSA was associated with good prognosis [3, 12]. After these reports on the usefulness of alternative antiandrogen therapy, this therapy has been commonly used in Japan. In addition, estrogen-related drugs, such as estramustine phosphate and ethinyl-estradiol, have also been used for post recurrence of alternative antiandrogen therapy. In particular, the usefulness of ethinyl-estradiol has been assessed in retrospective studies, and favorable results have been obtained, demonstrating PSA progression free survival (PFS) of 10 months in CRPC patients in Japan and PFS of 15.1 months in metastatic CRPC in western countries [4, 13]. Administration of low-dose estramustine phosphate for CRPC showed favorable response before docetaxel treatment (7.1-month median PFS, and 42-month overall survival in 31 patients with CPRC) [5]. Also for dexamethasone, which has been used extensively for CRPC in Japan because of benefit in treatment of CRPC [14], the usefulness has been reconfirmed by a prospective study in western countries comparing dexamethasone and prednisone for treatment of CRPC, in which PFS periods were 9.7 months and 5.1 months, respectively [15].

In western countries, prospective clinical studies of hormonal therapy combined with

docetaxel from the initial treatment for advanced prostate cancer (CHAARTED study & STAMPEDE study), compared to 44 months and 45 months in hormonal therapy alone groups, overall survival rates in docetaxel-hormonal therapy combination groups were 57.6 months and 60 months, respectively [16, 17]. Meanwhile, a retrospective study using the large J-CaP database (N = 5618) has reported overall survival rates of 80.4 months, 67.2 months, and 45.6 months for stages M1a (N = 224), M1b (N = 4386), and M1c (N = 278), respectively, while showing good survival even without docetaxel in the initial treatment [9]. Although there may also be racial differences in responsiveness to hormonal therapy [18], good survival rates in Japan may be attributable in part to traditional treatments (vintage hormonal therapy) for CRPC including alternative antiandrogen therapy.

New hormonal therapy

Enzalutamide, a second-generation antiandrogen, and abiraterone acetate, an adrenal androgen synthesis inhibitor, were added to the coverage of the national health insurance system in Japan in 2014, and have been available for unrestricted clinical use for treatment of CRPC. These two drugs have been demonstrated to be useful for treatment of CRPC, whether or not docetaxel is used, in clinical studies conducted in Japan and in western countries [19-25].

This paper briefly reviews the pathogenesis of CRPC and the mechanism of action of these two drugs against CRPC [26]. Prostate cancer becomes CRPC mainly via two mechanisms. One is adaptation, in which prostate cancer cells gradually adapt to a post-castration low-androgen environment through reactivation of androgen receptor (AR) (hypersensitive AR). The other is clonal selection, in which androgen-independent prostate cancer (AIPC) cells, which exist more or less originally, increase after castration. Prognosis of CRPC is considered to differ depending on which of the two mechanisms has played a major role in CRPC development. In the case of Japan, given the aforementioned fact that certain therapeutic effects are produced by switching among antiandrogen agents [3], CRPC presumably develops mainly though adaptation according to the result of alternative antiandrogen therapy [3]. More specifically, in a majority of prostate cancer cases that have advanced to CRPC, testosterone and DHT are considered to be synthesized from androgen of adrenal origin in a microenvironment in prostate cancer tissues and stimulate reactivated hypersensitive AR [27].

If hypersensitive AR can be inhibited more strongly, CRPC caused via adaptation is likely to be more effectively treatable. This is realized by the advent of the two new drugs for hormonal therapy. Enzalutamide shows about 8-times higher AR affinity than the

first-generation antiandrogen bicalutamide [28]. Furthermore, enzalutamide inhibits nuclear translocation of AR and also inhibits AR from binding to DNA by preventing the cofactor from binding to AR [28]. Abiraterone, on the other hand, inhibits androgen (DHEA) synthesis in the testis, adrenal gland, and prostate cancer tissues, decreases intracellular androgen levels, and inhibits AR activation. It is easy to understand if it is put this way; enzalutamide inhibits the downstream of AR more strongly, whereas abiraterone potently inhibits the upstream of AR. Nevertheless, enzalutamide and abiraterone may be equally effective in the sense that they basically inhibit the AR axis signaling pathway more strongly than conventional antiandrogens.

Indication of new hormonal therapies

In view of the pathogenesis of CRPC and the mechanism of action of the novel hormonal therapy drugs, it may be effective to start using these drugs as soon as the disease becomes CRPC. However, about 60% of patients are expected to enjoy improvements in prognosis by reducing PSA with vintage hormonal therapy as the initial treatment against CRPC such as alternative antiandrogen therapy [3]. In addition, when patient background was compared between in western countries and Japanese clinical studies using post-docetaxel abiraterone

and enzalutamide, vintage hormonal therapy was noticeably more commonly used among patients enrolled in studies in Japan (Fig. 1) [29]. The results from studies conducted in Japan showed the effectiveness of these drugs, although the efficacy of new hormone therapy agents was somewhat lower than that in in western countries studies [23, 24]. Western countries study has also suggested that the efficacy of abiraterone does not change appreciably depending on whether diethylstilboestrol (DES) is used [30]. Thus, if new drugs can be expected to be effective even after treatment with vintage hormonal therapy, is it necessary to use new drugs in a hurry? Rather, the final prognosis after CRPC may be improved by using new drugs after using vintage hormonal therapy. Conversely, if response and survival benefit can be expected from the use of vintage hormonal therapy, such as alternative antiandrogen therapy, after using potent new hormone therapy drugs, it may be also valid; however, unfortunately, this remains to be tested in clinical studies. It would be acceptable to use vintage hormonal therapy for 1 to 3 months and then decide whether to continue it or switch to some other treatment based on the change of PSA, and radiographic change, and symptom.

Moreover, there are some points to be aware of if new hormonal therapy drugs are to be used early in CRPC. It is a problem of drug resistance occurring due to long-term use. One of mechanisms for abiraterone/enzalutamide resistance is expression of an AR splicing variant

(AR-V7) [31, 32]. Studies in cultured cell systems have shown induction of AR-V7 expression due to increased RNA editing factors (U1A, U2A) after complete removal of androgen or addition of enzalutamide [33], suggesting the possibility that long-term strong inhibition of AR activation leads to increased expression of AR-V7 and affects prognosis. Enzalutamide/abiraterone converted AR-V7 positive in patients whose AR-V7 was initially undetectable [34]. Moreover, nuclear AR-V7 expression increased after enzalutamide/abiraterone in CRPC biopsy samples [35]. Among metastatic CRPC patients who received abiraterone or enzalutamide, OS and PSA-PFS in those positive for AR-V7 expression after the treatment have been reported to be significantly lower than in those with no expression [34]. If these drugs are to be started at an early stage of CRPC, physicians should be aware of the possibility of AR-V7 induction, although emergence of AR-V7 may be involved in other mechanisms.

Chemotherapy

Since the effectiveness of docetaxel against CRPC has been demonstrated [36, 37], docetaxel has become available for medical care under the national insurance system in Japan since 2008 [7]. While the maximum use of docetaxel is limited to 10 courses in western

countries, there are no restrictions on this respect in Japan and more than 10 courses of docetaxel can be used for some patients [38]. This may contribute to prolong prognosis for Japanese patients. However, long-term use of docetaxel in the standard regimen is not possible for many patients due to adverse effects, and biweekly administration of docetaxel has been reported to be effective and safe [39]. With this method, quality of life (QOL) during treatment with docetaxel is expected to be improved without losing the effectiveness of docetaxel.

However, treatment becomes difficult once docetaxel resistance develops. One of mechanisms for resistance to docetaxel is increased expression of P-glycoprotein from multiple drug resistant gene 1 (MDR1) [40]. P-glycoprotein is a cell membrane protein and has a function of extracellularly releasing docetaxel that has entered cells. Cabazitaxel is an anticancer agent effective against docetaxel-resistant prostate cancer [41]. Since cabazitaxel has low affinity to P-glycoprotein, it is not captured by P-glycoprotein even when its expression is enhanced by docetaxel, and thus is not easily released outside of cancer cells. The effectiveness of cabazitaxel against docetaxel-resistant prostate cancer has also been demonstrated in Japan. Since cabazitaxel has low affinity to P-glycoprotein, which is considered responsible for blood brain barrier, cabazitaxel is expected to be effective against

brain metastases [42, 43]. However, it remains controversial as to when is the best to switch docetaxel to cabazitaxel. In other words, it is difficult to judge how long to continue docetaxel and when to switch to cabazitaxel while docetaxel is still effective.

Recently reported results from CHAARTED and STAMPEDE trials have shown that overall survival was improved by using six courses of docetaxel from the initial androgen-deprivation therapy in prostate cancer patients with metastases [16, 17]. This hormonal chemotherapy from the initial treatment is now being established as a standard treatment in western countries. Yet this treatment cannot be performed currently in Japan because of insurance restrictions. This treatment may become available for patients in Japan someday, but then the patient selection would be a problem. I have formulated a hypothesis about why this treatment is effective for advanced prostate cancer [29]. This hormonal chemotherapy is thought to be useful for patients with high-level AIPC before treatment with low-AR expression. AIPC is speculated to be more in patients with a very high grade of malignancy [44, 45]. AR immunostaining with a pattern oriented approach for response was capable of accurately predicting response to hormone therapy in patients with advanced stage disease [46]. Hormonal chemotherapy may be effective, if it is performed selectively on such patients with low-AR expression.

Seesaw theory

Relapses after new hormonal therapy are treated with docetaxel or cabazitaxel, but for relapses after that, physicians would often perform BSC. However, new hormonal therapy rechallenge after chemotherapy can sometimes reduce PSA again and improve the situation. Onishi et al. described that ethinylestradiol rechallenge for CRPC lead to a prolonged disease control in selected patient [47]. Abiraterone acetate rechallenge also decreased PSA in heavily pre-treated CRPC patients [48]. We also observed the cases whose PSA was decreased by enzalutamide and abiraterone acetate after heavily pre-treatments including chemotherapy (Fig. 2). Although rechallenge is not applicable to all CRPC patients, hormonal therapy may be attempted before starting BSC. Similar phenomenon was observed in a patient who had metastatic anaplastic lymphoma kinase (*ALK*)-rearranged lung cancer, resistance to crizotinib developed because of a mutation in the *ALK* kinase domain [49]. They showed that clonal progression was related with resensitization to crizotinib against lorlatinib *ALK* Resistance Mutation L1198F [49]. I formulated the following hypothesis as to why rechallenge is effective for CRPC after some hormonal therapies and chemotherapy (Fig. 3). CRPC is in a situation where two clonal cell populations, hormone-hypersensitive prostate

cancer (HHSPC) and AIPC, are mixed. New hormonal therapy, of course, is only effective for HHSPC cells. Docetaxel may inhibit the proliferation of HHSPC in some degree. In contrast, COU-AA-301 trial and AFFIRM trial revealed HHSPC can survive after docetaxel treatment because abiraterone and enzalutamide were still effective after docetaxel [50, 51]. In other words, the effect of docetaxel is restrictive for HHSPC. On the other hands, new hormonal therapy decreases the number of HHSPC cells, but may be ineffective for AIPC. When chemotherapy is then performed, the number of AIPC cells decreases, but surviving HHSPC and stem cell-derived HSPC may increase again [52, 53]. If new hormonal therapy is performed thereafter again, HHSPC cells decrease and AIPC cells increase again. Eventually, AIPC cells become resistant to all treatments finally, and kill the patient. Alternating hormonal therapy and chemotherapy in this way causes changes in the ratio of HHSPC and AIPC cells, an effect that seems like seesaw (Seesaw theory). In addition, it is thought that prostatic cancer progresses further through interactions between HSPC and AIPC (our unpublished data). The above-mentioned CHAARTED and STAMPEDE trials may be effective presumably because HSPC and AIPC are simultaneously attacked by hormone chemotherapy and thus this seesaw does not move.

Border attack by Ra-223

Japanese health insurance started to cover the treatment of Radium-223 (Ra-223) for CRPC with bone metastasis in 2016. According to ALSYMPCA trial using Ra-223, Ra-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs. 11.2 months) [54]. Moreover, time to first symptomatic skeletal event (SSE) was longer with Ra-223 than with placebo (median 15.6 months *vs* 9.8 months) [55]. However, in Phase II study using Ra-223, a lot of cases that PSA was elevated were observed although Alp was decreased [56]. Even in Phase II study in Japan using Ra-223, the mean change rate of PSA by Ra-223 was rather increased to 97.3% and 230.5% although the mean change rate of Alp was -19.3% and -1.9% on 12 weeks after first treatment and 4 weeks after final treatment, respectively. We experienced the case that PSA continued being elevated although bone-derived Alp (BAP) and Bone Scan Index (BSI) on bone scintigraphy were improved by Ra-223 [57, 58]. It remains unclear why such discrepancy occurs by Ra-223. A feature of Ra-223 is to release alpha particle of which flying length is very short [59]. This is the reason why incidence of myelosuppression caused by Ra-223 is low compared with Sr-89. However, a short flying length of alpha particle was considered with a problem. Previously we studied the repression of osteoplastic bone metastases of the prostate cancer by bisphosphonate in

vivo [60]. We noticed that a lot of prostate caner cells still remained in bone marrow although bisphosphonate existing in the bone matrix could prevent cancer cells from infiltrating into a bone matrix at that time (Fig. 2 in reference Miwa et al. [60]). From this observation, we hypothesized that Ra-223 as well as bisphosphonate cannot destroy cancer cells existing in the remote area from a bone matrix distantly although alpha particles from Ra-223 kill cancer cells near the bone matrix. However, since prostate cancer cells living in the remote area from the bone matrix continues still secreting PSA, PSA may be elevated. This speculation may explain the discrepancy between PSA and BSI/Alp (Border attack by Ra-223). Post hoc analysis of ALYSYMPCA trial showed that median overall survival was also longer in patients who received Ra-223 plus abiraterone, enzalutamide, or both than in those who did not receive these agents [61]. Moreover, according to the result of ALSYMPCA trial, it is considered that it was the most effective to use Ra-223 for the patients with moderate bone metastases (Extent of disease score: 2 to 3 or 2-7% of BSI). When physicians use Ra-223 for bone metastasis, it will be necessary to evaluate the degree of bone metastasis exactly and consider concomitant drugs.

Evaluation of Image

A decline and an elevation of serum PSA value are the effective biomarker when physicians judge the regression and the recurrence of prostate cancer. However, they sometimes experience that a symptom of patients worsens and the results of the image are poor even if an absolute value of the PSA is low. Moreover, PSA value may not become the prognostic marker [62, 63]. Since advanced prostate cancer often metastasize to bone, it is extremely important to evaluate the change of bone metastasis. The extent of disease (EOD) on bone scintigraphy was used to stratify the level of bone metastasis [64]. However, it was difficult to monitor EOD quantitatively. Therefore, the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) recommends to use bone scintigraphy only for progression of bone metastasis [65]. Recently, a computer-aided diagnosis system (CAD) on bone scintigraphy has been developed for improving the interpretations of bone scan images. CAD shows Bone Scan Index (BSI) which provides a quantitative measure of the percentage of the adult skeleton involved by bone metastases [57, 66]. BSI on bone scintigraphy was a predictor of overall survival [67-69]. Measurement of BSI revealed that PSA is not always correlated with the level of bone metastasis [29]. PCWG3 also recommends computed tomography (CT) to evaluate lymph node metastases and visceral metastases [65]. It is extremely important to evaluate not only the PSA value but also various images regularly and to treat for CRPC.

Conclusion

When physicians choose the therapy for patients with CRPC, it is extremely important to judge comprehensively in consideration of (1) the effectiveness of therapeutic drugs based on evidence in Japan, (2) the PSA nadir level and the situation of the progress after CRPC, (3) treatment responsiveness for vintage and new hormonal therapy, (4) the evaluation with the image, (5) the adverse event by the treatment.

Conflicts of Interest: All authors have no competing interest.

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Figure legends

Fig. 1 The comparison of antiandrogen lines number in the clinical trial of new hormonal therapies between foreign countries and Japan. **A.** Clinical trial of abiraterone acetate after docetaxel treatment. **B.** Clinical trial of enzalutamide after docetaxel treatment. This figure was modified from an article written by Mizokami et al. [29].

Fig. 2 Rechallenge of hormonal therapy after chemotherapy. A. The case that enzalutamide (Enz) was successful later using docetaxel (DOC), dexamethasone (DEX), TAK-700 (Orteronel, a CYP17A1 inhibitor like abiraterone acetate, was used in Phase II clinical study), Enz, and cabazitaxel (Cab) sequentially. B. The case that abiraterone was successful later using bicalutamide (Bic), flutamide (Flu), estramustine phosphate (EMT), ethinyl-estradiol (Ethinyl-E2), DOC, Enz, ITK-1 (peptide vaccine Phase III clinical study, DEX vs DEX + peptide vaccine) [70], and Cab sequentially.

Fig. 3 Seesaw theory. **A.** Prostate cancer tissue, especially CRPC tissue is heterogeneous including androgen-hypersensitive cells and androgen-independent cells. Hormonal therapies can attack androgen-hypersensitive cells but not androgen-independent cells. Although chemotherapy can attack androgen-independent cells and androgen-hypersensitive cells, the effect of chemotherapy on androgen-hypersensitive cells is weak. **B.** Androgen-hypersensitive cells increase during chemotherapy. **C.** Androgen-independent cells increase during hormonal therapy. **D.** Androgen-hypersensitive cells increase during other chemotherapy again.

Fig. 1

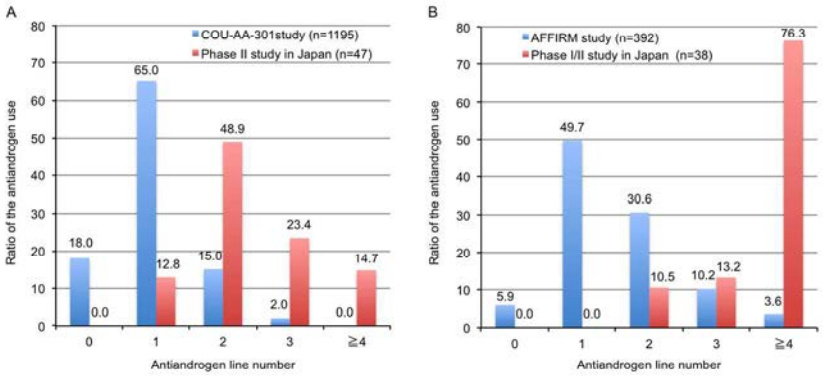

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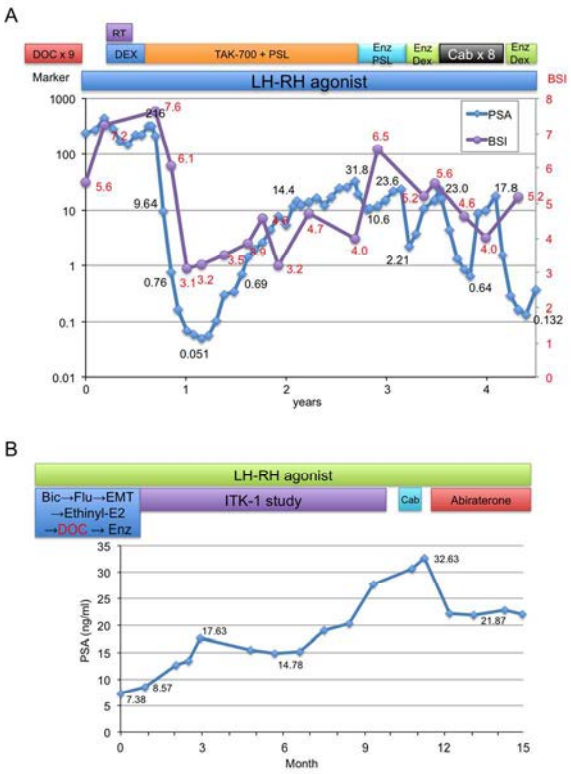
Fig. 2



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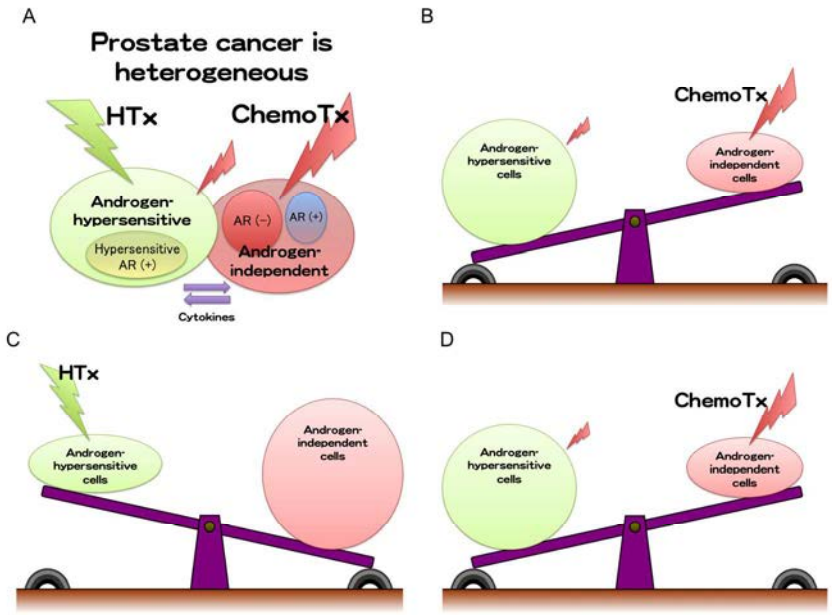

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