European Review for Medical and Pharmacological Sciences 2013; 17: 1658-1664

Taxane- and epothilone-based chemotherapy: from molecule cargo cytoskeletal logistics to management of castration-resistant prostate carcinoma

C. ALBERTI

L.D. of Surgical Semeiotics, Parma, Italy

Abstract. – Challenges in the discovery of more potent agents to treat the castration-resistant prostate carcinoma (CRPC) reflect the frustrating condition due to development of its drug-resistance in addition to hormone-refractoriness. Although among the different CRPC therapy modalities, the chemotherapy regimens might seem conceptually outclassed as exhibiting a scant tumor cell-selectivity if compared with new molecular mechanism-based agents (so-called "smart drugs"), nevertheless, combo-therapies which combine the chemotherapeutic highly killing potential with specific mechanism-targeting products, seem to be effective antitumor measures. Thus, both microtubule (taxanes, epothilones, noscapine, Vinca-derivatives) and actin filament (pertenotoxins, cytochalasin D)-targeting agents may supply valuable outcomes in CRPC, either alone or in combination with "smart drugs" such as tyrosine- or multi-kinase receptor blockers, mTOR (mammalian target of rapamicin) inhibitors, monoclonal antibodies against various growth factor signaling receptors. Among the microtubule-inhibiting drugs, taxanes are able, by binding the tubulin, to cause polymerization and stabilization of the microtubules with following suppression of their dynamic properties at the mitotic spindle, that results in cancer cell cycle block at G2/M phase together with apoptosis. Cabazitaxel, a novel taxane-based agent, unlike other taxane compounds, exhibits low propensity for P-glycoprotein (Pgp)-mediated plasmalemmal drug efflux pump, thus, avoiding the development of taxane-resistance. Epothylones are a family of novel microtubule-targeting drugs, like taxane inhibiting microtubule dynamic behaviour at mitotic spindle and, therefore, preventing cancer cells from mitosis. Unlike docetaxel and paclitaxel, epothilones maintain their cytotoxic performance even in cancer overexpressing Pgp. Epothilone B-promoted radiosensitivity enhancement has been shown in radioresistant human prostate cancer cells, because such agent is able to delay DNA- strand break repair together with prolonging cell cycle block. To insightfully understand either microtubule or actin filament meshwork-targeting drug pharmacodynamics, functional cytoskeletal features such as cytoskeleton-related molecule cargo logistics, are preliminary taken into consideration.

Key Words:
Nanotechnology, Cytoskeletal logistics, Androgen resistance, Cancer stem cells, Radiation therapy.

Introduction

Prostate carcinoma (PC) is the most common and second most letal male cancer in USA and European countries, although most recently both diagnostic and therapeutic advances have been made in lowering its mortality[1]. Despite initial organ-confined tumor therapy with surgery or radiation, sometimes PC runs into a recurrence that temporarily may be controlled by androgen-deprivation modalities. Even though such treatment, both reducing blood testosterone levels through Gn-RH pituitary receptor agonists (triptorelin, leuprorelin, goserelin, buserelin) or antagonists (Degarelix, Abarelix), and preventing DHT (dihydrotestosterone)-binding to peripheral nuclear androgen receptor (AR) through anti-androgens (bicalutamide, nicalutamide, flutamide, MDV 3100, the last showing an effectiveness even in bicalutamide -resistant PC), might induce a rapid biochemical/clinical responses, inescapably, after an average of 18 to 24 months, the disease becomes refractory to hormone therapy – *castration-resistant prostate carcinoma*, CRPC – with subsequently a median survival of 12 to 18 months[2-8]. CRPC refers to the condition of prostate cancer growth at castrate androgen levels (serum testosterone less than 50 ng/ml), biochemically shown by a continuous PSA rise, on three consecutive measurements, after antiandrogen withdrawal for at least 28 days or following an additional secondary hormone manipulation.

Constant efforts are in progress to identify new cancer cell, either molecular or structural, targets towards which direct more effective therapeutical measures[3-5].

Corresponding Author: Contardo Alberti, MD; e-mail: eneide94@gmail.com

Overall View on Both Current and Emerging Novel Therapies in CRPC

First and foremost, it has been pointed out, in several clinical experiences, that the progression from hormone-dependent to hormone-independent PC may be delayed by intermittent androgen-deprivation therapy and, on the other hand, as soon as a biochemical relapse arises, the antiandrogen (flutamide) withdrawal may sometimes induce a temporary decline in blood PSA levels. But the unreliability and the transience of such effects suggest a timely carrying out of more suitable current approaches mean-while looking at pipeline measures, all together including:

- Combination of estrogens (ethinyl-estradiol) and somatostatin analogs (lanreotide, pasireotide) as neuroendocrine targeting therapy, to affect, besides the tumor cells, also their microenvironment that can play an antiapoptotic role[9];
- Inhibition over 17-α-hydroxylase/17-20 lyase (Cyp17)-aromatase through abiraterone, a selective blocker of adrenal androgen generation[10,11];
- *Chemotherapy with cytotoxic drugs*, among which cytoskeleton-targeted agents such as Vinca alkaloids (vinblastine, vinorelbine, vinflumine), noscapine, taxanes and epothilones, pertenotoxins[4,12-17];
- Molecular mechanism-based strategy with "smart drugs" capable of either blocking cell proliferation signaling pathways or inducing apoptosis. To the former group belong receptor tyrosine- kinase or multikinase inhibitors among which those interfering with HER-1 (human epidermal growth factor receptor-1, EGFR), HER-2 (human epidermal growth factor receptor-2, also called c-erbB-2/*neu* as a omolog of the rat *neu* oncogene), PDGFR (plateled-derived growth factor receptor), VEGFR (vascular endothelial growth factor receptor) whereas to the latter group, recombinant TRAIL (tumor necrosis factor-related apoptosis inducing ligand) and poly (ADP-ribose) polymerase (PARP) inhibitors[2,3,13,16,18,19] Death cell receptor-mediated anoikis/apoptosis seems to be also achieved, according to recent studies, by quinazoline-derived α_1-adrenoceptor antagonists[19,20-23]. Also the inhibition of IGF-1R signaling (Insulin-like growth factor-1 receptor® → activation of both $MAPK_S$, mitogen-activated protein kinases, and PI3K, phosphatidil-inositol 3-kinase/AKT) can exert cancer cell growth decrease. Regarding it, anti-IGF-1R antibodies may provide tumor growth inhibitory effects[2,19]. VEGFR multikinase inhibitors (Sorafenib, Sunitinib) as well as anti-VEGF monoclonal antibodies (Bevacizumab) or VEGF-decoy receptor Aflibercept, by playing an antiangiogenic role, may induce indirect antitumoral effects[19,25,26].
- Bone (metastasis)-targeted therapy through either RANKL (receptor activator of NF-kB ligand) antagonist Denosumab or endothelin-A receptor antagonist Atrasentan[2,12,24-26]; also bone-seeking α-emitter Ra-223 seems to be useful, intravenously administered, in bone metastatic CRPC;
- Immunotherapy: anti-prostate cancer autologous dendritic cell-based vaccine (e.g., Sipuleucel-T, made-up of autologous dendritic cells loaded *ex vivo* with PAP, prostatic acid phosphatase, tumor-associated antigen), anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody Ipilimubab[27-30], to overcome chemotherapy-resistance;
- Gene-therapy on the basis of gene expression profiling: replacement or inactivation of defective genes, induction of cell death by adenovirus-mediated delivery of pro-apoptotic Mda-7/IL-24 gene, cytoreductive gene-treatment, gene-silencing by interfering short RNA_S[31-33];
- Epigene-therapy through hystone-deacetylase inhibitors, such as suberoylanilide, or DNA-methyltransferase blockers[18,34];
- Targeting the pluripotent stem cell (PSC)-like cancer cells as expressing PSC-transcription factors such as OCT3/4 and SOX2, that can start the prostate tumorigenesis[35].

Cytoskeletal Molecule Cargo Logistics

The cytoskeletal complex includes cell interior microtubules and cell cortex actin microfilaments together with wide microtrabecular reticulum. The *microtubules* are hollow cylindrical structures, whose wall is made up of a series of small protein heterodimeric subunits, a negatively charged α-tubulin and a positively charged β-tubulin, thus, such dimer sets acting as dipoles. Showing a dynamic plastic behaviour, they are capable of self-polymerization or, instead, self-depolymerization, depending on the various cell conditions. The energy needed for their polymerization is supplied by GTP (guanosine triphosphate) hydrolysis to GDP. *Actin microfilaments* are helicoidal temporary structures – dissipative structures – of G-actin globular protein, which rapidly develop, by polymerization, from a cytosolic stock of their subunits, and, just as rapidly

dissolve as soon as they are no longer necessary. The energy required for their polymerization is provided by ATP (adenosine triphosphate) hydrolysis to ADP. Some drugs are able to specifically enhance or inhibit both microtubule- and actin microfilament-polymerization. The *microtrabecular reticulum* consists of 3-D intertwined actin filament network, that interconnects all cell structures including the nucleus cytoskeleton and chromosomes, with following feed-back control system between nucleus and cytoplasm, moreover contributing to intra-cell dynamic organization of organelles.

Cytoskeletal functions exceed that of sheer mechanical cell scaffold, because the cytoskeleton plays an important role in cell contractility, cytokinetics and, given its links with the inner part of plasmalemmal receptors, in intra-cell signal transduction[36]. Microtubules, as filamentary oscillating structures (Fröhlich's coherent vibrations), cooperate with mitochondria in generating cell electromagnetic fields.

Molecular motors that transport molecule cargoes – protein complexes, receptor-ligand sets, secretory vesicles, organelles – along the cytoskeleton, include myosin family compounds, running on cell cortex actin filaments, and kinesin/cytoplasmic dynein, travelling on cell interior microtubules, both paths representing polarized mono-rails for the cargo bidirectional, either endocytic or exocytic, translocation, mean-while the motor proteins converting the ATP-to-ADP-hydrolysis-derived energy into motion[37,38].

The *endocytosis* plays a leading role in plasmalemmal receptor-ligand complex internalization, thus driving extra-cell molecular signals to induce specific changes in gene expression[39]. That's how occurs also for the stepwise endocytic movements, along actin-to-tubulin pathway, of several signaling receptors, such as HER-1, HER-2 and other growth factor receptors[40,41].

In both endocytic and exocytic routes, selective logistic mechanisms put the vesicular cargoes with high specificity dependently on their *coat protein components* (clathrin, COP-I and COP-II) while *protein adaptors* are able to bind cargoes to specific coat pits[40,41]. Moreover, to allow a selective recruitment of protein cargoes from the cytosol, *membrane lipids*, acting as specific "rafts", sort them at sequential steps of both endocytic and exocytic paths[42]. Just like this, the tyrosine kinase receptors, through a specific endocytic lipid rafts, are brought to the endoplasmic reticulum where PI3P (phosphatidylinositol-3, 4, 5-triphosphate), is synthesized, triggering, in turn, the PI3P/AKT-mTOR signaling pathway.

Quite recently, it has been demonstrated that TFEB (transcriptor factor EB), a master gene for lysosomal biogenesis, coordinates the whole logistics of autophagic pathway, from the formation of autophagosomes (cell scavenger organelles) and their intracell ride to fusion with the lysosomes, where the substrate degradation is performed[43].

The *biochemical pattern* of cytoskeletal molecule cargo translocation must be today integrated with a *biophysical model*, where charged particles (electrons, protons, ions), photons (optical and infraoptical radiations) and quantized vibrational-mechanical waves are looked as signal-messengers travelling on the cytoskeloton. Furthermore, microtubules, as electrical polar structures – oriented dipoles – are able to direct the molecule cargoes towards specific targets, their charge-energy resulting from GTP (guanosine triphosphate) hydrolysis to GDP. What's more, a fraction of such energy can induce cytoskeleton vibrations with following generation of electromagnetic fields. Just in this regard, some mechanisms of malignancy – anoikis of cancer cells, local invasion and distant metastasis – may be assumed as dependent on the cell abnormal electromagnetic influences[36,44].

Cytoskeleton Targeting Chemotherapy

Until the mid-1990$_s$, CRPC was considered refractory to chemotherapy regimens while afterwards it has been demonstrated that the mitoxantrone-prednisone combined treatment can have a palliative effectiveness in CRPC-diseased men. Seven years ago, taxane (docetaxel)-based chemotherapy showed to carry a significant survival advantage in CRPC, further improved by recent resorting to cabazitaxel[13,14]. Efforts intended to develop novel agents capable of overcoming drug resistance-related mechanisms have led to try the effectiveness of epothilones in taxane-refractory tumours.

Among the microtubule-inhibiting drugs, *taxanes* – docetaxel, paclitaxel, cabazitaxel – are able, by binding the tubulin, to cause microtubule polymerization-stabilization with following suppression of their dynamic properties at the mitotic spindle, that induces cancer cell mitotic arrest (cell cycle block at G2/M phase) and apoptosis[45-47].

Survival benefit achieved by docetaxel-based chemotherapy in patients with CRPC have denied

the burden of CRPC as a chemoresistant cancer[48]. However, tumors characterized by P-glycoprotein (Pgp) overexpression show usually a docetaxel-refractoriness. Cabazitaxel, a novel taxane drug, unlike other taxane-based agents, exhibits low propensity for Pgp-mediated plasmalemmal drug efflux pump, thus avoiding the development of taxane-resistance, therefore showing an antitumor activity even in docetaxel-resistant CRPC. Cabazitaxel combined with prednisone can induce a median survival of 15.1 months, compared with that of 12.7 months achieved through mitoxantrone, as it results from phase III-TROPIC trial[3,14,49-51].

Intriguingly, in the treatment of CRPC, microtubule-targeted taxane chemotherapy seems also to interfere with androgen-mediated signaling because taxanes may prevent the androgen-dependent nuclear translocation of the androgen-receptor (AR) by targeting AR connection with tubulin[52]. In fact AR, in the absence of ligand DHT, is primarly located, bound with Hsp90 (heat shock protein 90) chaperone, onto the cytoskeleton, while the link with the ligand results in AR homodimerisation and translocation in the nucleus, where binds to specific androgen-dependent genes with following proliferative and trophic effects. Incidentally, Hsp90 chaperone plays a critical role in prostate cancer cell survival response to chemotherapy and radiation, whereas Hsp90 inhibitors, such as I7-AAG (17-allylamino-17-demethoxygeldanamycin), can sensitize cancer cells to cytotoxic agents, including taxanes and *radiation therapy*[53].

RNA_i (RNA interfering)-mediated STMN1 microtubule-gene silencing can have synergistic effects with paclitaxel against the prostate cancer cells[54]. Also histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid, potentiate the taxane (docetaxel) anticancer activity in CRPC, by both acetylating tubulin and inhibiting Bcl-2 antiapoptotic protein[34].

Unfortunately, cremophor, a nonionic polyethoxylated castor oil used as solubilizer/emulsifier of taxanes, has been associated with severe hypersensitivity reactions, sometimes including anaphylaxis and cardiac collapse. Recently, to avoid such drawbacks, it has been shown that paclitaxel delivery in cancer cells may result significantly enhanced by its binding with *albumin-nanoparticles* (Abraxane)[54,55]. Nevertheless, endotoxin-like properties of taxol in itself, such as macrofage activation with production of inflammatory cytokines and nitric oxide, can induce hypersensitivity conditions.

Epothilones are a family of novel microtubule-targeting agents originally identified as metabolites of myxobacterium *Sorangium cellulosum*. Like taxanes, epothilones stabilize the microtubules and inhibit their dynamic function at the mitotic spindle, thus preventing cancer cells from mitosis. Particularly, once epothilones bind to α/β-tubulin subunit, the rate of its dissociation decreases with following tubulin polymerization, hence microtubule stabilization and suppression of microtubule detachment from centrosomes, with cell cycle arrest at the G2/M transition phase[48,60-63].

Both semisynthetic and total-synthetic epothilone analogs (ixabepilone, sagopilone, patupilone), currently undergoing various clinical develpment phases to treat different cancers, exhibit a cytotoxic activity even towards taxane-refractory cancer cell lines, without showing taxane-like endotoxin-properties[48,60-63].

Differences between epothilones and taxanes in drug-resistance mechanisms have been elucidated by recent research findings on the which basis epothilone cytotoxicity appears to be unaffected by alanine-to-threonine substitution at reside 364 – microtubule β-tubulin which, instead, is responsible for chemoinsensitivity to taxanes. It follows that epothilones, unlike taxanes, maintain their cytotoxic performance even in cancers overexpressing Pgp.

Given their good water solubility, epothilones do no need cremophor-based solvents sometimes causing hypersensitivity reactions[48,61,62].

It has been demonstrated an epothilone-induced radiosensitivity enhancement in *radioresistant human prostate cancer cells*, because such agent is able to delay DNA-strand break repair together with prolonging cell cycle arrest and enhancing cell death[63].

Noscapine, a microtubule-modulating alkaloid, displays synergistic effects with docetaxel in anticancer chemotherapy, moreover exhibiting cytotoxic activity even in paclitaxel-resistant tumors[15,64].

Pertenotoxins, besides targeting cytoskeletal actin, can induce apoptotic effects by increasing caspase-3 activity together with poly (ADP-ribose) polymerase (PARP) cleavage[17].

Implications for Current Approaches and Future Research Directions

Although among the different CRPC therapy modalities, the chemotherapy regimens might appear conceptually outclassed as exhibiting a scant tumor cell-selectivity if compared with new molecular mechanism-targeting agents – so-called smart

drugs – nevertheless "combo-strategies", that combine the chemotherapeutic highly killing potential with specific mechanism-based products, seem to be effective antitumor measures, moreover allowing a lower cytotoxic drug doses with following more limited drug-related toxic side effects. So, both microtubule (taxanes, epothilones, Vinca-derivatives)- and actin filament meshwork (pertenotoxins, cytochalasin D)-targeting agents may supply valuable outcomes in CRPC – as well as in other advanced malignancies – either alone or in combination with "smart drugs" such as tyrosine- or multi-kinase receptor blockers, mTOR (mammalian target of rapamicin) inhibitors, monoclonal antibodies against various growth factor signaling receptors[48,65,70].

Currently, other cytoskeleton targeting products are under investigation to use them in cancer chemotherapy, among which some antimycotics (benomyl, griseofulvin) and antimicrobials (sulfonamides), that, what's more, seem to exhibit less toxic side effects than taxanes and Vinca alcaloids[67].

Recent studies show that microtubule-targeting drugs, besides the suppression of microtubule dinamics with following cell cycle arrest at G2/M phase, can promote cell apoptosis via intrinsic mitochondrial, cell death-receptor-independent, pathway by inducing the translocation of Bax (Bcl associated x-protein) from cytosol into mitochondria and, sequentially, Bak (Bcl-2 antagonist killer) mitochondrial protein activation with release into cytosol of some pro-apoptotic factors such as Mg^{2+}-dependent endonuclease G and SMAC (second mitochondria-derived activator of caspase), that, in turn, promote the 9 → 3 caspase cascade[68,69].

As far as *taxanes* are concerned, it's now arousing a great interest that their microtubule-inhibiting effects may be enhanced by *albumin nanoparticle carriers* that, moreover, allow to avoid the use of solubilizing cremophors sometimes inducing severe hypersensitivity effects[54,72]. Other nanoparticle – based carriers, such as nanoporous silicon particles, for chemotherapeutic shutting, have been recently proposed[72].

Epothilones, as well as other microtubule-stabilizing agents (taxanes, noscapine), prolong activation of the spindle assembly checkpoint with following cancer cell death in mitosis, and, in addition, show a certain activity also in truly taxane-refractory patient cohorts, thus representing a potential therapeutic niche when a Ppg-induced taxane-resistance unfortunately develops[70]. It has also been demonstrated an epothilone *B-induced radiosensitivity enhancement* in radiorefractory prostate cancer cells, however the radiation therapy resulting to be excluded from the treatment of metastatic CRPC while it might have therapeutic effects on locally-advanced CRPC[63].

The application of chemotherapy regimens in CRPC, as well as of other anticancer modalities, requires a preventive assessment of their possible effectiveness, individually considering tumor distant invasive propensity, about it today playing an important role the detection of both *circulating prostate cancer cells* through PSAmRNA/RT-PCRC (reverse transcriptase-polymerase chain reaction) assay and, more thoroughly, *circulating cancer stem cells* (CSC_S) responsible for resistance to chemotherapy and radiation. Indeed, cancer cells expressing pluripotent stem cell transcription factors, such as OCT3/4 and SOX2, exhibit quite uncontrollable aggressive aptitudes[35].

Conclusions

The development of techniques capable of molecularly identifying prostate CSC_S not only may provide relevant predictive informations to make proper clinical-therapeutic decisions, together with allowing potential indications of efficacy, but also can entail the expansion of studies on CSC-targeted drugs[3,71,73]. The constant strong challenges in the discovery of more and more efficacious agents to manage CRPC, moreover tailoring the treatment to the individual patient gene-molecular cancer cell features, reflect the frustrating condition due to drug-resistance development in addition to hormone-refractoriness[73,75].

Conflict of Interest

None to declare.

References

1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. Ca Cancer J Clin 2011; 61: 69-90.
2) van der Poel HG. Smart drugs in prostate cancer. Eur Urol 2004; 45: 1-17.
3) Vishnu P, Tan WW. Update on options for treatment of metastatic castration-resistant prostate cancer. Onco Target Ther 2010; 24: 39-51.
4) Albiges L, Loriot Y, Gross-Goupil M, de La Motte Rouge T, Blesius A, Escudier B, Massard C, Fizazi K. New drugs in metastatic castration-resistant prostate cancer. Bull Cancer 2010; 97: 149-159.
5) Wu Y, Rosenberg JE, Taplin ME. Novel agents and new therapeutics in castration-resistant prostate cancer. Curr Opin Oncol 2011; 23: 290-296.

6) Kirby RS, Fitzpatrick JM, Clarke N. Abarelix and other Gn-RH antagonists in prostate cancer. BJU Int 2009; 104: 1580-1584.

7) Sonesson A, Rasmussen BB. *In vitro* studies investigation the interactions between Degarelix and Cytochrome P450. Basic Clin Pharmacol Toxicol 2011; 109: 195-202.

8) Vasaitis TS, Njar VC. Novel potent anti-androgens of therapeutic potential: recent advances and developments. Future Med Chem 2010; 2: 667-680.

9) Sciarra A, Innocenzi M, Ravaziol M, Minisola F, Alfarone A, Cattarino S, Monti G, Gentile V, Di Silverio F. Neuroendocrine target therapies for prostate cancer. Urologia 2011; 78: 137-141.

10) Massard C, Fizaki T. Targeting continued androgen receptor signaling in prostate cancer. Clin Cancer Res 2011; 17: 3876-3883.

11) Attard G, Reid AH, Olmos D, de Bono JS. Antitumor activity with CYP17 blockade indicates that CRPC frequently remains hormone driven. Cancer Res 2009; 15: 4937-4940.

12) Sonpavde G, Sternberg CN. Contemporary management of metastatic castration-resistant prostate cancer. Curr Opin Urol 2011; 21: 241-247.

13) Kim SJ, Kim I. Current treatment strategies for castration-resistant prostate cancer. Korean J Urol 2011; 52: 157-165.

14) Ansari J, Hussain SA, Alhasso A, Mahmood R, Ansari A, Glah J. Role of second-line systemic treatment post-docetaxel in metastatic CRPC: current strategies and future directions. Anticancer Agents Med Chem 2011; 11: 296-306.

15) Mahmoudian M, Rahimi-Moghoddam P. The anticancer activity of noscapine: a review. Rec Pat Anticancer Drug Disc 2009; 4: 92-97.

16) Fleming M, Sonpavde G, Kondagunta GV, Galsky M, Hutson Th E, Sternberg CN. Systemic therapy and novel agents for metastatic castration-resistant prostate cancer. Update Cancer Ther 2009; 3: 133-145.

17) Kim MO, Moon DO, Heo MS, Lee JD, Jung JH, Kim SK, Choi YH, Kim GY. Pertenotoxin-2 abolishes activated NF-κB leading to suppression of NF-κB gene products and potentiation of apoptosis. Cancer Lett 2008; 271: 25-33.

18) Antonarakis ES, Carducci MA, Eisenberg MA. Novel targeted therapeutics for metastatic castration-resistant prostate cancer. Cancer Lett 2010; 291: 1-13.

19) Ullrich A. Molecular targets in cancer therapy and their impact on cancer management. Oncology 2002; 63(Suppl 1): 1-5.

20) Kyprianou N. Doxazosin and terazosin suppress prostate growth by inducing apoptosis: clinical significance. J Urol 2003; 169: 1520-1525.

21) Sakamoto S, Schwarze S, Kyprianou N. Anoikis disruption of focal adhesion-Akt signaling impairs renal cell carcinoma. Eur Urol 2011; 59: 734-744.

22) Hori Y, Ishii K, Kanda H, Iwamoto Y, Nishikawa K, Soga N, Kise H, Arima K, Sugimura Y. Naftodipil, a selective alpha 1- adrenoceptor antagonist, suppresses human prostate tumor growth by altering interactions between tumor cells and stroma. Cancer Prev Res 2011; 4: 87-96.

23) Alberti C. Apoptosis induction by quinazoline-derived alpha1-blockers in prostate cancer cells: biomolecular implications and clinical relevance. Eur Rev Med Pharmacol Sci 2007; 11: 59-64.

24) Lebret T, Méjean A, Houédé N. Physiopathology and new therapeutic strategies in the management of bone metastases of prostate cancer. Progr Urol 2011; 21: 301-307.

25) Abdulla A, Kapoor A. Emerging novel therapies in the treatment of castrate-resistant prostate cancer. Can Urol Assoc 2011; 5: 120-133.

26) Nabhan C, Parsons B, Touloukian EZ, Stadler WM. Novel approaches and future directions in castration-resistant prostate cancer. Ann Oncol 2011; 22: 1948-1957.

27) Cheever MA, Higano C. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA approved therapeutic cancer vaccine. Clin Cancer Res 2011; 17: 3520-3526.

28) May KF, Grilley JL, Drake Ch G, Dranoff G, Kantoff PW. Prostate cancer immunotherapy. Clin Cancer Res 2011; 17: 5233-5238.

29) Mori T. Ipilimumab, a new molecular targeted therapy of malignant neoplastic disease. Gan To Kagaku Ryoho 2011; 38: 31-35.

30) Madam RA, Pal SK, Sartor O, Dahut WL. Overcoming chemotherapy resistance in prostate cancer. Clin Cancer Res 2011; 17: 3892-3901.

31) Bangma CH, Mongiat P, Kraau R, Schenk-Braat E. Gene therapy in urology: strategies to translate theory into practice. BJU Int 2005; 96: 1163-1170.

32) De Fougerolles A, Vornlocher HP, Maraganore J, Liebnerman J. Interfering with disease: a progress report siRNA-based therapeutics. Nat Rev Drug Discov 2007; 6: 443-453.

33) Greco A, di Benedetto A, Howard CM, Kelly S, Nande R, Dementieva Y, Miranda M, Brunetti A, Salvatore M, Claudio L, Sarkar D, Dent P, Curiel DT, Fisher PB, Claudio PP. Eradication of therapy-resistant human prostate tumors using an ultrasound-guided site-specific cancer terminator virus-delivery approach. Mol Ther 2010; 18: 295-306.

34) Hwang JJ, Kim YS, Kim MJ, Kim DE, Jeong IG, Kim CS. Histone deacetylase inhibitor potentiates anticancer effect of docetaxel via modulation of Bcl-2 family proteins and tubulin in hormone refractory prostate cells. J Urol 2010; 184: 2557-2564.

35) Bae KM, Su Z, Frye C, McClellan S, Allan RW, Andrejewski JT, Kelley V, Jorgensen M, Steindler DA, Viewegt J, Siemann DW. Expression of pluripotent stem cell reprogramming factors by prostate tumor initiating cells. J Urol 2010; 183: 2045-2053.

36) Bistolfi F. The bioconductive connectional system. In: Bistolfi F. Biostructures and radiations: order-disorder. Torino. Minerva Medica 1991; 53-60.

37) Ross JL, Ali MY, Warshaw DM. Cargo transport: molecular motors navigate a complex cytoskeleton. Curr Opin Cell Biol 2008; 20: 41-47.

38) Goldman RD, Grin B, Mendez MG, Kuczmarski ER. Intermediate filaments: versatile building blocks of cell structure. Curr Opin Cell Biol 2008; 20: 28-34.

39) Miaczynska M, Pelkmans L, Zerial M. Not just a sink: endosomes in control of signal transduction. Curr Opin Cell Biol 2004; 16: 400-406.

40) Watanabe TM, Higuchi H. Stepwise movements in vesicle transport of HER-2 by motor proteins in living-cells. Biophys J 2007; 20: 4109-4120.

41) Owen DJ. Linking endocytic cargo to clathrin: structural and functional insights into coated vesicle formation. Biochem Soc Trans 2004; 32: 1-14.

42) van Meer G, Sprong H. Membrane lipids and vesicular traffic. Curr Opin Cell Biol 2004: 16: 373-378.

43) Settembre C, Di Malta C, Polito VA, Arencibia MG, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, Sordiello M, Rubinsztein DC, Ballabio A. TFEB links autophagy to lysosomal biogenesis. Science 2011; 332: 1429-1433.

44) Pokorny J, Hasek J, Vanis J, Jelinek F. Biophysical aspects of cancer-electromagnetic mechanism. Indian Exp Biol 2008; 46: 310-321.

45) Yue QX, Liu X, Guo DA. Microtubule-binding natural products for cancer therapy. Planta Med 2010; 76: 1037-1043.

46) Alberti C. Cytoskeleton structure and dynamic behaviour: quick excursus from basic molecular mechanisms to some implications in cancer chemotherapy. Eur Rev Med Pharmacol Sci 2009; 13: 13-21.

47) Pasquier E, Kavallaris M. Microtubules: a dynamic target in cancer therapy. IUBMB Life 2008; 68: 165-170.

48) Bhandary MS, Hussain M. Epothilones and the new generation of phase 3 trials for prostate cancer. BJU Int 2005; 96: 296-302.

49) de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO. Prednisone plus cabazitaxel or mitoxantrone for metastatic CRPC progressing after docetaxel treatment. Lancet 2010; 376: 1147-1154.

50) Oudard S. TROPIC: phase 3 trial of cabazitaxel for treatment of metastatic castration-resistant prostate cancer. Future Oncol 2011; 7: 497-506.

51) Bouchet BP, Galmarini CM. Cabazitaxel, a new taxane with favorable properties. Drugs Today 2010; 46: 735-742.

52) Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. Cancer Res 2010; 70: 7992-8002.

53) Solit DB, Scher HI, Rosen N. Hsp90 as therapeutic target in prostate cancer. Sem Oncol 2003; 30: 709-716.

54) Zhou Q, Ching AK, Leung WK, Szeto CY, Ho SM, Chan PK, Yuan YF, Lai PB, Yeo W, Wong N. Novel therapeutic potential in targeting microtubules by nanoparticle albumin-bound paclitaxel in hepatocellular carcinoma. Int J Oncol 2011; 38: 721-731.

55) Kratz F. Albumin, a versatile carrier in oncology. Int J Clin Pharmacol Ther 2010; 48: 453-455.

56) Kamath K, Jordan MA. Suppression of microtubule dynamics by epothilone B is associated with mitotic arrest. Cancer Res 2003; 63: 6026-6031.

57) Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. J Clin Oncol 2004: 2015-2025.

58) Muhlradt PF, Sasse F. Epothilone B stabilizes microtubuli of macrophages like taxol without showing taxol-like endotoxin activity. Cancer Res 1997; 57: 3344-3350.

59) Ganguly A, Yang H, Cabral F. Paclitaxel-dependent cell lines reveal a novel drug activity. Mol Cancer Ther 2010; 9: 2914-2923.

60) Bystricky B, Chau I. Patupilone in cancer treatment. Expert Opin Investig Drugs 2011; 20: 107-117.

61) Kowalski RJ, Giannakakon P, Hamel E. Activities of the microtubule-stabilizing agents epothilones A and B with purified tubulin and in cells resistant to paclitaxel. J Biol Chem 1997; 272: 2534-2541.

62) Julien B, Shah S. Heterologous expression of epithilone biosynthetic genes in Myxococcus xanthus. Antimicrob Agents Chemother 2002; 46: 2772-2778.

63) Kong Z, Raghavan P, Xie D, Boike T, Burma S, Chen D, Chakraborty A, Hsieh JT, Saha D. Epothilone B confers radiation dose enhancement in DAB2IP gene knock-down radioresistant prostate cancer cells. Int J Radiat Biol Biophys 2010; 78: 1210-1218.

64) Pannu V, Karna P, Sajja HK, Shukla D, Aneja R. Synergistic antimicrotubule therapy for prostate cancer. Biochem Pharmacol 2011; 81: 478-487.

65) Carlson RO. New tubulin-targeting agents currently in clinical development. Expert Opin Investig Drugs 2008; 17: 707-722.

66) Kim M, Liao J, Dowling ML, Voong KR, Parker SE, Wang S, El-Deiry WS, Kao GD. TRAIL inactivates the mitotic checkpoint and potentiates death induced by microtubule-targeting agents in human man cancer cells. Cancer Res 2008; 68: 3440-3449.

67) Singh P, Rathinasami K, Mohan R, Panda D. Microtubule assembly and dynamics: an attractive target for anticancer drugs. IUBMB Life 2008; 60: 368-375.

68) Zimmermann KG, Bonzon C, Green OR. The machinery of programmed cell death. Pharmacol Ther 2001; 92: 57-70.

69) Rovini A, Savri A, Braguer D, Carré M. Microtubule-targeted agents: when mitochondria become essential to chemotherapy. Biochem Biophys Acta 2011; 1807: 679-688.

70) Harrison M, Swanton C. Epothilones and new analogues of microtubule modulators in taxane-resistant disease. Expert Opin Invest Drugs 2008; 17: 523-546.

71) Danila M, Fleisher M, Scher HI. Circulating tumor cells as biomarkers in prostate cancer. Clin Cancer Res 2011; 17: 3903-3912.

72) Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer 2005; 5: 161-171.

73) Wicha MS, Hayes DF. Circulating tumor cells: not all detected cells are bad and not all bad cells are detected. J Clin Oncol 2011; 29: 1508-1510.

74) Evans AJ, Ryan P, Van Derkwast T. Treatment effects in the prostate including those associated with traditional and emerging therapies. Adv Anat Pathol 2011; 18: 281-293.

75) Attard G, de Bono J. Translating scientific advancement into clinical benefit for CRPC patients. Clin Cancer Res 2011; 17: 3867-3875.