OncoImmunology 2:8, e26084; August 2013; © 2013 Landes Bioscience

New immunotherapeutic paradigms for castration-resistant prostate cancer

Lorenzo Galluzzi

Gustave Roussy; Villejuif, France; Université Paris Descartes/Paris V, Sorbonne Paris Cité; Paris, France;
Equipe 11 labelisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers; Paris, France

Keywords: ^{223}Ra, alpharadin, docetaxel, Provenge®, sipuleucel-T, Xofigo®

Abbreviations: DC, dendritic cell; CRPC, castration-resistant prostate cancer; SSE, symptomatic skeletal event

Prostate cancer nowadays represents the first leading cause of cancer-related deaths among men in the UK, the second in US (after lung cancer) and the sixth worldwide.[1] The risk of developing prostate cancer (as well as several other malignancies) progressively increases with age, the average age of patients at diagnosis being 70.[2] According to current estimates, more than 80% of men will develop prostate cancer by the age of 80. However, the actual incidence of this malignancy cannot be precisely assessed, as several cases never become clinically manifest owing to the death of patients for cancer-unrelated causes. Indeed, malignant lesions of the prostate generally progress at a slow pace and early stage neoplasms are associated with few, if any, symptoms.[3,4] Many factors have been tentatively implicated in the etiology of prostate cancer, including genetic alterations as well as viral, alimentary and sexual determinants. However, while convincing evidence links some of these factors, such as *BRCA1* and *BRCA2* mutations (which also predispose to the development of breast and ovarian carcinoma), to an increased risk of developing prostate cancer,[5] other causal correlations, such as that with a xenotropic MuLV-related virus, have been officially discarded.[6,7]

Upon diagnosis of prostate cancer, the first therapeutic decision relates to whether treatment is actually needed. As most of these neoplasms afflict the elderly (often exhibiting several co-morbidities) and progress very slowly, the risk of overtreatment is indeed relatively high. It has been suggested that in 50–75% of cases, prostate cancer does not cause any harm before death for other causes intervenes.[8] A reduced fraction of patients, however, present with aggressive lesions at a young age (50–60), calling for the delineation of a therapeutic strategy. The most appropriate therapeutic option for the management of prostate carcinoma obviously depends on several tumor-related parameters such as stage, Gleason score and prostate-specific antigen (PSA) circulating levels, as well as on the age and general health status of the patient.[3,4] Of note, a large fraction of patients is eligible for active surveillance, entailing the careful observation of the neoplasm over time until signs of progression (which may never manifest). Conversely, subjects bearing aggressive prostate cancers are generally treated with radical prostatectomy (if eligible) combined with cryotherapy or radiation therapy (in the case of localized lesions), or with chemotherapy and/or hormonal therapy (in the case of metastatic disease).[3,4] Unfortunately, most hormone-dependent cancers eventually become refractory to androgen deprivation and often metastasize to the bones.[9] Until 2004, no therapeutic options that would prolong the survival of patients affected by castration-resistant prostate cancer (CRPC) were available, a situation that has significantly evolved throughout the last decade.

Nowadays, several chemotherapeutic agents have been shown to prolong the overall survival of CRPC patients, including docetaxel (a taxane that stabilizes microtubules, hence exerting prominent antimitotic effects),[10] which is most often employed as a first-line intervention, or cabazitaxel (a synthetic taxane derivative),[11] which is prefentially used in docetaxel-resistant CRPC patients.[12] Conversely, the great expectations that had been generated by Phase II clinical trials investigating the therapeutic profile of docetaxel, prednisone and bevacizumab (a vascular endothelial growth factor [VEGF]-neutralizing monoclonal antibody)[13,14] have been recently mitigated by Phase III data.[15-17] Of note, the most efficient therapeutic option against CRPC available to date is represented by Provenge® (sipuleucel-T, from Dendreon Corp.), a dendritic cell (DC)-enriched autologous cell preparation activated ex vivo with a recombinant variant of prostate acid phosphatase (PAP) fused to granulocyte macrophage colony-stimulating factor (GM-CSF).[18,19] In Phase III clinical trials, Provenge® has indeed been associated with a favorable safety profile as well as with a median survival benefit of 4.1 mo.[18,19] This compares favorably with the therapeutic profile of docetaxel, which provokes mild-to-severe side effects in a fraction of patients and provides a median survival advantage of 2–3 mo.[10] A meticulous phenotypic characterization of the cellular components of Provenge® has

*Correspondence to: Lorenzo Galluzzi; Email: deadoc@vodafone.it
Submitted: 06/26/2013; Accepted: 06/26/2013
Citation: Galluzzi L. New immunotherapeutic paradigms for castration-resistant prostate cancer. OncoImmunology 2013; 2:e26084

not been performed to date. Nonetheless, this immunotherapeutic product has been approved by the FDA for the therapy of asymptomatic or minimally symptomatic metastatic CRPC patients in 2010, de facto representing the first (and thus far only) DC-based preparation licensed by regulatory agencies for use in humans.[20-22]

On May, 15th 2013, Bayer HealthCare announced that the FDA approved Xofigo® (an injectable solution of ^{223}Ra chloride also known as Bay88–8223 or alpharadin) for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease (source http://press.healthcare.bayer.com/). This decision matured along with the accumulation of promising safety and efficacy results by multiple Phase II clinical trials completed in the past 5 y,[23-25] and followed the disclosure of Phase III data obtained in the context of the ALSYMPCA trial (NCT00699751). This multicenter, randomized, double-blind study (enrolling 921 patients from more than 100 centers in 19 countries) confirmed indeed the favorable safety profile of Xofigo® and suggested that this radiotherapeutic agent may provide an overall survival benefit to CRPC patients of 2.8 mo.[26] In addition, the interim analysis revealed that Xofigo® (compared with best standard of care) significantly delays the first symptomatic skeletal event (SSE). Of note, $^{223}Ra^{+}$ ions mimic Ca^{2+} ions in their ability to form complexes with hydroxyapatite at areas of increased bone turnover, such as metastatic lesions.[26] Xofigo® is therefore characterized by a pronounced osteophylic nature, which explains (at least in part) its favorable toxicological profile.[25,26] In line with previous observations,[25] common (> 10% of cases) adverse reactions in patients receiving Xofigo® in the context of the ALSYMPCA trial were nausea, diarrhea, vomiting and peripheral edema, whereas the most frequent hematologic abnormalities were anemia, lymphocytopenia, leukopenia, thrombocytopenia and neutropenia.[26]

During the last decade, the conceptual foundations of anticancer radiotherapy have been significantly reconsidered. A consistent amount of preclinical and clinical data has indeed suggested that the efficacy of this therapeutic modality not only reflects the cytostatic and cytotoxic effects of ionizing radiation, but also involves a prominent immunological component.[27] A striking phenomenon in support of this notion is the so-called "abscopal effect," consisting in the development of objective responses to radiotherapy by non-irradiated (out-of-field) neoplastic lesions.[28] At least in experimental tumor models, the abscopal effect is mediated by the immune system.[28] Radiotherapy has also been shown to trigger immunogenic cell death (ICD), a particular type of apoptosis that elicits adaptive immune responses.[29] It is therefore tempting to speculate, yet remains to be formally demonstrated, that the abscopal effect may reflect the ICD-inducing potential of ionizing rays. Irrespective of these incognita, it will be interesting to see whether combining Xofigo® with other immunotherapeutic interventions such as Provenge® and docetaxel (which also appears to trigger ICD, or at least some of its main hallmarks)[30,31] will provide further survival benefits to CRPC patients. The approval of Xofigo® may have opened promising avenues for the treatment of prostate cancer.

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; PMID:21296855; http://dx.doi.org/10.3322/caac.20107
2. Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, Ries LA, Merrill RM, Kaplan RS. Cancer surveillance series: interpreting trends in prostate cancer--part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst 1999; 91:1017-24; PMID:10379964; http://dx.doi.org/10.1093/jnci/91.12.1017
3. D'Amico AV. Risk-based management of prostate cancer. N Engl J Med 2011; 365:169-71; PMID:21751910; http://dx.doi.org/10.1056/NEJMe1103829
4. Schröder FH, Roach M 3rd, Scardino P. Clinical decisions. Management of prostate cancer. N Engl J Med 2008; 359:2605-9; PMID:19073981; http://dx.doi.org/10.1056/NEJMclde0805491
5. Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997; 336:1401-8; PMID:9145676; http://dx.doi.org/10.1056/NEJM199705153362001
6. Retraction AB. Science 2011; 334:1636
7. Retraction. Identification of a novel gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant. PLoS Pathog 2012; 8:
8. Bangma CH, Roemeling S, Schröder FH. Overdiagnosis and overtreatment of early detected prostate cancer. World J Urol 2007; 25:3-9; PMID:17364211; http://dx.doi.org/10.1007/s00345-007-0145-z
9. Seruga B, Ocana A, Tannock IF. Drug resistance in metastatic castration-resistant prostate cancer. Nature reviews. Clin Oncol 2011; 8:12-23
10. Galsky MD, Vogelzang NJ. Docetaxel-based combination therapy for castration-resistant prostate cancer. Ann Oncol 2010; 21:2135-44; http://dx.doi.org/10.1093/annonc/mdq050
11. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, et al.; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:1147-54; PMID:20888992; http://dx.doi.org/10.1016/S0140-6736(10)61389-X
12. Jilani A, George E, Adler AI. NICE guidance on cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Lancet Oncol 2012; 13:573-4; PMID:22833888; http://dx.doi.org/10.1016/S1470-2045(12)70220-6
13. Vacchelli E, Eggermont A, Galon J, Sautès-Fridman C, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2013; 2:e22789; PMID:23482847; http://dx.doi.org/10.4161/onci.22789
14. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zucman-Rossi J, Zitvogel L, Kroemer G. Trial Watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938
15. Ross RW, Galsky MD, Febbo P, Barry M, Richie JP, Xie W, Fennessy FM, Bhatt RS, Hayes J, Choueiri TK, et al. Phase 2 study of neoadjuvant docetaxel plus bevacizumab in patients with high-risk localized prostate cancer: a Prostate Cancer Clinical Trials Consortium trial. Cancer 2012; 118:4777-84; PMID:22282219; http://dx.doi.org/10.1002/cncr.27416
16. Ning YM, Gulley JL, Arlen PM, Woo S, Steinberg SM, Wright JJ, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2010; 28:2070-6; http://dx.doi.org/10.1200/JCO.2009.25.4524
17. Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, Stadler WM, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol 2012; 30:1534-40; http://dx.doi.org/10.1200/JCO.2011.39.4767
18. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, Kantoff PW. Sipuleucel-T. Nat Rev Drug Discov 2010; 9:513-4; PMID:20592741; http://dx.doi.org/10.1038/nrd3220
19. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, et al.; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-22; PMID:20818862; http://dx.doi.org/10.1056/NEJMoa1001294

20. Vacchelli E, Eggermont A, Fridman WH, Galon J, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238
21. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zitvogel L, Kroemer G. Trial Watch: Adoptive cell transfer immunotherapy. Oncoimmunology 2012; 1:306-15; PMID:22737606; http://dx.doi.org/10.4161/onci.19549
22. Galluzzi L, Senovilla L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, Zitvogel L, Kroemer G. Trial watch: Dendritic cell-based interventions for cancer therapy. Oncoimmunology 2012; 1:1111-34; PMID:23170259; http://dx.doi.org/10.4161/onci.21494
23. Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germá JR, O'Bryan-Tear CG, Haider T, Hoskin P. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013; 63:189-97; PMID:23000088; http://dx.doi.org/10.1016/j.eururo.2012.09.008
24. Nilsson S, Strang P, Aksnes AK, Franzèn L, Olivier P, Pecking A, Staffurth J, Vasanthan S, Andersson C, Bruland ØS. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 2012; 48:678-86; PMID:22341993; http://dx.doi.org/10.1016/j.ejca.2011.12.023
25. Nilsson S, Franzén L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennernäs B, Petersson U, Johannessen DC, Sokal M, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 2007; 8:587-94; PMID:17544845; http://dx.doi.org/10.1016/S1470-2045(07)70147-X
26. Vogelzang NJ, Helle SI, Johannessen DC, O'Sullivan JM, Garcia-Vargas JE, O'Bryan-Tear CG, et al. Efficacy and safety of radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases who did or did not receive prior docetaxel (D) in the phase III ALSYMPCA trial. J Clin Oncol 2013; 31:Abstr 5068.
27. Vacchelli E, Vitale I, Eggermont A, Sautes-Fridman C, Galon J, Tartour E, et al. Trial Watch: Anticancer radioimmunotherapy. OncoImmunology 2013; 2: Forthcoming; http://dx.doi.org/10.4161/onci.24238
28. Kroemer G, Zitvogel L. Abscopal but desirable: The contribution of immune responses to the efficacy of radiotherapy. Oncoimmunology 2012; 1:407-8; PMID:22754758; http://dx.doi.org/10.4161/onci.20074
29. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-032712-100008
30. Senovilla L, Vitale I, Martins I, Kepp O, Galluzzi L, Zitvogel L, Castedo M, Kroemer G. An anticancer therapy-elicited immunosurveillance system that eliminates tetraploid cells. Oncoimmunology 2013; 2:e22409; PMID:23482968; http://dx.doi.org/10.4161/onci.22409
31. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, Galluzzi L, Adjemian S, Kepp O, Niso-Santano M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science 2012; 337:1678-84; PMID:23019653; http://dx.doi.org/10.1126/science.1224922