Critical Reviews in Oncology/Hematology 97 (2016) 231–237

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

"Hit the primary": A paradigm shift in the treatment of metastatic prostate cancer?

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Contents

ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form 24 August 2015
Accepted 26 August 2015

Keywords:
Metastatic prostate cancer
Definitive treatments of the primary tumour
Local radiotherapy

ABSTRACT

Patients with metastatic prostate cancer (PC) represent a heterogeneous group with survival rates varying between 13 and 75 months. The current standard treatment in this setting is hormonal therapy, with or without docetaxel-based chemotherapy. In the era of individualized medicine, however, maximizing treatment options, especially in long-term surviving patients with limited disease burden, is of capital importance. Emerging data, mainly from retrospective surgical series, show survival benefits in men diagnosed with metastatic PC following definitive therapy for the prostate. Whether the irradiation of primary tumor in a metastatic disease might improve the therapeutic ratio in association with systemic treatments remains investigational. In this scenario, modern radiation therapy (RT) can play a significant role owing to its intrinsic capability to act as a more general immune response modifier, as well as to the potentially better toxicity profile compared to surgery. Preclinical data, clinical experience, and challenges in local treatment in *de novo* metastatic PC are reviewed and discussed.

1. Introduction

Local control of the primary tumor in the presence of metastatic disease has been associated with improved outcome in several malignancies (Flanigan et al., 2001; Mickisch et al., 2001; Temple et al., 2004). Metastatic renal cell carcinoma could be considered a paradigm in this field: indeed, two phase III trials clearly demonstrated better overall survival (OS) rates in patients treated with radical nephrectomy and interferon-alpha compared to patients receiving systemic treatment alone (Flanigan et al., 2001; Mickisch et al., 2001).

In prostate cancer (PC), evidence from three large prospective randomized phase III trials suggest that, in patients with locally advanced tumors at high risk of occult micrometastatic disease, adding radiotherapy (RT) to androgen deprivation therapy (ADT) significantly improves 10-year outcome (D'Angelillo et al., 2015; Mottet et al., 2012; Warde et al., 2011; Widmark et al., 2009). Reduction in the cancer-specific and overall mortality rates (Warde et al., 2011; Widmark et al., 2009), as well as improvements in loco-regional control and distant metastases-free progression (Mottet

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http://dx.doi.org/10.1016/j.critrevonc.2015.08.023
1040-8428/

Nomenclature

ADT	Androgen deprivation therapy
APCs	Antigen-presenting cells
BT	Brachytherapy
CI	Confidence interval
CSM	Cancer-specific mortality
CSS	Cancer-specific survival
CTCs	Circulating tumor cells
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
DCs	Dendritic cells
DSS	Disease-specific survival
EBRT	External beam radiotherapy
GM-CSF	Ggranulocyte-macrophage colony-stimulating factor
HR	Hazard ratio
IGRT	Image-guided radiotherapy
LH-RH	Luteinizing hormone –relasing hormone
LT	Local treatment of the primary tumor
MCRPC	Metastatic castration resistant prostate cancer
NLT	Non-local treatment of the primary tumor
NSR	No surgery or radiation therapy
OS	Overall survival
PAP	Prostatic acid phosphatase
PC	Prostate cancer
PD-1	Programmed cell death protein-1
PFS	Progression-free survival
PSA	Prostate specific antigen
QoL	Quality of life
RP	Radical prostatectomy
RT	Radiotherapy
SEER	Surveillance epidemiology and end results
SIB	Simultaneous integrated boost
TILs	Tumor-infiltrating lymphocytes

et al., 2012), were observed in the combined modality, starting to emerge early, 3 years after randomization.

On the other hand, in multi-metastatic PC patients (T1-4, N0-1, M1) the role of local control of the primary remains unclear, with ADT using LHRH analogues/antagonists, with or without docetaxel, representing the treatment of choice as recommended by current guidelines (Heidenreich et al., 2014). Although the scientific evidence supporting ADT in metastatic PC patients remains weak, in the case of proven metastatic disease, ADT is considered the up-front standard treatment (Heidenreich et al., 2014). ADT is not curative, but might frequently provide rapid relief of symptoms and a good rate of "temporary" biochemical control.

While the role of local RT as palliative treatment for bleeding or obstruction is well described, the benefit of associating RT to ADT as first-line treatment to improve the therapeutic ratio in metastatic PC patients remains investigational. Such an approach seems to be supported by compelling evidences indicating that patients with a limited number of PC metastases, thus entering the so-called oligometastatic state — an intermediate state of tumor spread with limited metastatic capacity (Weichselbaum and Hellman, 2011) — have a better prognosis compared with those with extensive metastatic disease (Schweizer et al., 2013; Ost et al., 2014).

The aim of the present critical review is to report and discuss available data on the role of prostate irradiation in de novo hormone-naïve metastatic PC patients. Due to the paucity and heterogeneity of data published in the recent literature, our review was not conducted according to a properly performed systematic protocol, but rather represents an overview of the body of knowledge on this topic.

2. Preclinical data

The challenging issue of local irradiation in metastatic PC is whether the natural history of disease progression might be positively influenced, once metastases have developed, by reclaiming the organ of tumor origin.

An answer comes from the experimental demonstration of a process called 'tumor self-seeding' (Kim et al., 2009), during which circulating tumor cells (CTCs) — usually seeding distant organs — have the potential to reinfiltrate an established tumor at the primary site. Under these circumstances, tumor growth and progression may be favored if the primary tumor remains locally untreated despite the metastatic disease. Conversely, this reseeding phenomenon could not occur when malignant cells encounter an unfavorable growth environment, such as when the primary tumor is controlled (removed or irradiated).

What really might contribute to a change in the role of RT in the metastatic setting is based on some radiation-induced immunological responses, a phenomenon called "abscopal effect", consisting in the regression of distant disease after a localized treatment of the primary tumor (Demaria et al., 2004). Abscopal effects are most often attributed to the activation of the antitumor immunity, which, unlike site-specific RT, can have broader systemic effects.

Traditionally, RT has been considered a local treatment only. The abscopal effect is proof of the systemic effects of RT (Formenti and Demaria, 2009), and it is triggered by a T cell-mediated and antigen-specific (Demaria et al., 2004, 2005) immune reactions as a consequence of the processing, by macrophages and dendritic cells (DCs), of antigens released during tumor necrosis caused by RT, eliciting tumor-specific CD8+ T cells. The local inflammation induced by RT activates several complex local immunological reactions contributing to better antigen cross-presentation and immune activation, finally leading to CD8+ cytolytic T cell responses (Friedman, 2002; Reits et al., 2006). In other words, danger signals associated with the effects of ionizing radiation could convert the irradiated tumor into an immunogenic hub becoming, in some patients, a very efficient individualized in situ vaccine (Demaria et al., 2004). Once this "vaccination" has taken place, the host's immune response contributes both to the local response to RT and to a systemic rejection of metastases (Formenti and Demaria, 2009).

Intriguingly, a prerequisite for eliciting an antitumor immune response is that tumor-ablative RT doses are delivered by stereotactic body radiation therapy (SBRT), likely because only when RT is applied in this form immunomodulatory effects triggered by inflammation and apoptosis recruit DCs to the irradiated site (Seung et al., 2012; Rubner et al., 2012). A hint of the potential ability of SBRT in evoking the abscopal effect can be found in the favorable results of some series (Ponti et al., 2015; Jereczek-Fossa et al., 2012; Schick et al., 2013) — also confirmed in recent reviews — reporting data on this strategy in the treatment of nodal PC metastases (Ost et al., 2015; De Bari et al., 2014): it may be argued that, despite the very likely presence of micrometastatic disease around the macroscopically involved nodes, higher doses per fraction delivered to the target lesion might result curative on the nearest microscopic disease by the activation of the abscopal effect.

An indirect confirmation of these immune-modulated responses is the role gradually being acquired by modern immunotherapy in defeating the established tolerance toward the cancer and restoring an effective tumor-specific immune response (Quinn et al., 2015; Santoni et al., 2014). At the forefront of this strategy has been the development of Ipilimumab (Hodi et al., 2010), a monoclonal antibody which blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a checkpoint receptor that inhibits T cell activation. Associated with palliative radiation, this drug has been shown to increase OS in patients with advanced melanoma (Grimaldi et al., 2014; Postow