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Critical Reviews in Oncology/Hematology 93 (2015) 136–148

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era

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Received 14 February 2014; received in revised form 18 August 2014; accepted 1 October 2014

Contents

Abstract

Currently, androgen deprivation therapy (ADT) has a well-defined role when administered together with radiotherapy (RT): neo-adjuvant and concurrent combination for intermediate risk-disease and adjuvant therapy for high risk disease. Evidence of this association was generated by randomized trials designed and led approximately 30 years ago; thus the question which arises is how relevant and portable are these data in our current clinical practice?

In the present review, we examine the pitfalls of these published randomized controlled trials, their relevance to present daily clinics, where high-dose external beam RT or brachytherapy is applied, as well as the adoption of ADT in patients with concomitant cardiovascular disorders.

Keywords: Prostate cancer; Radiotherapy; Androgen deprivation therapy; Brachytherapy.

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http://dx.doi.org/10.1016/j.critrevonc.2014.10.003
1040-8428/

1. Rationale and background

Radiotherapy (RT) has been used for localized prostate cancer (PCa) for nearly a century [1]. In the dose escalation era, despite excellent outcomes after primary external beam radiotherapy (EBRT)+/− hormonal therapy for localized PCa, a proportion of patients with localized disease experienced a biochemical relapse [2–5]. This failure rate is related to well-known predictive factors [PSA, Gleason Score (GS), T-stage], as well as to intrinsic tumor radio-resistance and micro-metastatic disease at diagnosis [6–8]. Dose-escalated RT and agents enhancing radiation effect could significantly improve results. The use of hormonal therapy in PCa gained traction after the study by Huggins and Hodges [9] which demonstrated the androgen dependence of prostatic cells. Thereafter, pharmacologic castration was the preferred alternative to surgical castration, due to the advantages of avoiding potential orchiectomy-related psychological effects, as well as the ability to restore the integrity of the hypothalamic–pituitary–testicular axis. Initially, androgen deprivation therapy (ADT) employed estrogens (diethylstilbestrol) [10]; however, the high rate of cardiovascular morbidity and mortality, due to first-pass hepatic metabolism and the formation of thrombogenic metabolites, led to a dramatic decrease in its use [11,12]. While ADT was considered the mainstay of treatment in metastatic disease [13,14], several randomized trials supported its use in combination with External-Beam Radiation Therapy (EBRT) for localized PCa and unfavorable risk features [15–18]. LH-RH agonists represent the benchmark in RT + ADT combination, although various classes of drugs, including LH-RH antagonists and anti-androgens, are currently available.

The rationale of RT + ADT combination is based on the ability of androgen suppression to cause involutional changes in PCa cells and reduce tumor volume. Androgen ablation causes an 80% reduction in the number of epithelial cells in the normal prostate within 10 days, due to apoptotic cell death [19]. The pronounced dependence on androgen, however, is substantially mitigated in PCa, where the predominant effect of androgen ablation seems related to the inhibition of cell proliferation rather than apoptosis [20], resulting in a shift to quiescence [21], which in turn could theoretically diminish radiation sensitivity. The hypothesis that androgen ablation may act as a radiosensitizer despite the shift to quiescence has been confirmed in clinical trials showing that the combined use of radiation plus androgen ablation is superior than when used separately. [22–24]. This was initially proven in animal models demonstrating enhanced tumor control when ADT was incorporated to radiation within a neoadjuvant setting. Zietman et al. [25,26] showed that the radiation dose required to control tumors grown in nude mice decreased when the tumors were pretreated with androgen ablation: a reduction in the dose required to eliminate 50% of the tumor from 89 Gy with radiation alone to 60 Gy with orchiectomy followed by radiation one day later was observed. More pronounced dose reductions (42 Gy) were seen when RT was delayed for 12 days after orchiectomy, but the same results were not observed when radiation preceded ADT.

Joon et al. [27] showed a supra-additive interaction between androgen ablation and radiation through modulation of apoptosis. This effect was dependent on the timing of the two treatments, since the time course of apoptotic response to RT is conserved when androgen ablation precedes radiation. A crucial factor accounting for treatment failure and poor prognosis of PCa could be the anomalous and inefficient pattern of vascularization, leading to intermittent/chronic hypoxia [28,29]. Since inadequate tissue oxygenation is the prime trigger of angiogenesis, in which several angiogenic factors – including vascular endothelial growth factor and its receptors – are expressed [30], androgen deprivation can play a role in down regulating the expression of vascular endothelial growth factor, inducing apoptosis of endothelial cells and consequently decreasing vascularization [31–33]. ADT, therefore, may restore a transient "normalization" of tumour vascularization either by reducing leaky immature tumour vessels, causing perivascular cell deaths, decreasing interstitial pressure and increasing oxygenation, mostly during the neoadjuvant period [34]. A further field of interest is the monitoring of changes in tumor hypoxia during ADT: Hypoxia-inducible factor 1 (HIF1) is a transcription factor of high importance for PCa progression [35] and recent studies have shown that its suppression can play a significant role in ADT response without detectable changes in hypoxic fraction. Moreover, the expression of its alpha subunit (HIF1a) can act as a hypoxia biomarker in PCa [36], which could be helpful for planning RT initiation and potential use of hypoxia-targeted therapy.

Currently, RT + ADT is a frequent combination therapy, but the adoption of dose escalated RT [2–5], along with long-term adverse effects of testosterone suppression [37–40], are considered crucial when identifying patients warranting the use of no, short-, or long-term ADT.

2. ADT and EBRT in prostate cancer

Two major settings in combining ADT and EBRT can be defined: short-course ADT, given in neoadjuvant and concurrent intermediate-risk disease, and long-term ADT, given adjuvantly for 2–3 years in high and very high-risk patients [41].

2.1. Short- course ADT and intermediate risk disease

Five published trials investigating short-course ADT recorded a benefit for neoadjuvant and concurrent ADT over RT alone, increasing ADT prescription in the United States from 5% in 1989 to 85% in 2002 (Table 1) [42,43].

In RTOG 94-08 trial [44], 1979 patients with organ-confined PCa and PSA $\leq$20 ng/ml were randomized to radiotherapy only (66.6 Gy/1.8 daily fractionation) or to