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Original article

Hypofractionation with simultaneous boost in breast cancer patients receiving adjuvant chemotherapy: A prospective evaluation of a case series and review of the literature

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ABSTRACT

Introduction: To evaluate acute toxicity and cosmetic outcomes of hypofractionated simultaneous integrated boost (SIB) as adjuvant treatment after breast-conserving surgery and adjuvant chemotherapy and to review the association of chemotherapy and short fractionation with boost.
Materials and methods: Patients presenting early-stage breast cancer were enrolled in a phase II trial. All patients received VMAT-SIB technique to the whole breast and tumor bed in 15 fractions, for a total dose of 40.5 and 48 Gy. Acute and late skin toxicities and breast pain were recorded. Cosmetic outcomes were also assessed as excellent/good or fair/poor.
Results: Between August 2010 and December 2015, 787 consecutive patients were treated and had at least 2 year follow-up. A subset of 175 patients underwent adjuvant chemotherapy (median age of 55 years) and was analysed. The median follow up was 39 months (range 24–80). At the end of RT treatment, skin toxicity was G1 in 51.1% of patients, G2 in 9.7%. At 2 years of follow up, it was G1 in 13.5% of patients, no cases $\geq$ G2; cosmetic outcome was excellent in 63.5% and good in 36.5% of the patients. No significant difference compared to the patients without systemic therapy was observed.
Conclusion: Hypofractionated VMAT-SIB in patients who had undergone adjuvant systemic therapy was safe and well tolerated in terms of acute and early late settings and cosmesis. Our data confirmed the results of other studies published on the association of hypofractionation and chemotherapy or concomitant boost.

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1. Introduction

In patients treated with breast-conserving surgery (BCS), radiotherapy (RT) plays a significant role in terms of both local control and breast cancer specific survival, as reported in a meta-analysis of 17 randomized trials [1]. In most of these clinical trials, RT was delivered by using conventional fractionation. During the past decade, mature results from phase III randomized trials conducted in the United Kingdom and Canada demonstrated comparable clinical outcomes and toxicity profiles between conventional and hypofractionated whole-breast irradiation (HF-WBI) [2,3] without strong evidence about the association of HF-WBI and chemotherapy. In the Canadian trial only 11% of the enrolled patients received adjuvant chemotherapy [2], while in the START-B and START-A respectively 21% (233/1110) and 36% (534/1487) of the patients in the hypofractionated arms had been subjected to chemotherapy [4,5].

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Different studies were published on HF-WBI including patients who had undergone adjuvant chemotherapy [6–11] and, specifically, two of them reported a separate assessment of this subgroup [12,13].

Other published experiences described the association between locoregional treatment using hypofractionated schedules and adjuvant chemotherapy [14,15].

Furthermore, several authors investigated the factors involved in the use of HF-WBI and showed that patients characteristics (particularly, age and chemotherapy receipt) and physician attitudes play a crucial role in this scenario [16–19].

Based on these data, recently, the American Society for Radiation Oncology (ASTRO) released an update on evidence based guideline supporting the use of HF-WBI also for patients who received chemotherapy [20].

On the other hand, the use of sequential or concomitant boost in patients treated with HF-WBI is still debated and unclear.

We previously reported on our Phase II trial on early stage breast irradiation with hypofractionated simultaneous integrated boost (SIB) and volumetric modulated arc therapy (VMAT) technique [21]. Based on this cohort, in the current analysis we assessed and evaluated skin toxicity and cosmetic outcome in the subset of patients who received chemotherapy. We also review and discuss about the association of chemotherapy and HF-WBI with boost.

2. Materials and methods

2.1. Patient characteristics

Patients with early stage breast carcinoma after conservative surgery were enrolled in an institutional phase II prospective non-randomized trial of adjuvant radiotherapy with SIB delivered with VMAT (VMAT-SIB). The study received the approval by the Ethical Review Committee (N. 708), in compliance with the Helsinki declaration. Informed consent was obtained from all individual patients. Selection criteria included age >18 years old, invasive cancer or ductal carcinoma in situ (DCIS), AJCC Stage I-II (T-size $\leq$3 cm, N $\leq$ 3), BCS, any systemic therapy (neoadjuvant or adjuvant).

The patients selected for the current analysis were treated according to the protocol, and had a follow-up time of at least 24 months. DCIS patients were excluded from the analysed group.

2.2. Treatment characteristics

2.2.1. Systemic therapy

On the basis of the primary tumor characteristics, hormonal receptor status, HER-2 status and/or age, patients were candidates for systemic adjuvant therapy according to departmental treatment policy. The treatment choice was the result of an interdisciplinary discussion among oncologists, surgeons, radiotherapists and pathologists.

Most patients received anthracycline regimen (AC: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four courses, or FEC: F-fluorouracil 500 mg/m^2 plus Epidoxorubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for four or six cycles).

The addition of taxanes to standard anthracycline should be considered for patients with more extensive disease burden or triple-negative disease. In this case patients after four cycles of AC received docetaxel 100 mg/m^2 $\times$4 cycles.

In case of comorbidities or patients' preference, i.v. CMF for a duration of six courses 1–8,q28 was considered (i.e. cyclophosphamide 600 mg/m^2, methotrexate 60 mg/m^2 and F-fluorouracil 600 mg/m^2).

All HER-2-positive breast cancers were treated with trastuzumab every 21 days for 1 year.

In patients with HER2-positive, node-negative disease and T-size <2 cm, a nonanthracycline regimen comprising paclitaxel 80 mg/m^2 weekly plus trastuzumab 4 mg/kg loading dose followed by 2 mg/kg for 3 months, and then one year of trastuzumab is indicated, while for more extensive disease treatment should commence with anthracycline and be followed by concurrent taxane and trastuzumab, with the trastuzumab continued for a total of 1 year.

2.2.2. Radiotherapy

Full details of the radiation treatment delivered according to the clinical protocol have been previously published [21]. Shortly, all patients were set-up in supine position, with both arms above the head. CT dataset was acquired with 3 mm thick adjacent slices. The clinical target volume (CTV) of the whole breast was the entire mammary gland. CTV of the boost was the surgical bed, defined by adding 1 cm to the surgical clips placed in the lumpectomy cavity during surgery. Planning target volumes (PTV) were contoured by adding a 5 mm margin to each CTV; PTVs were limited to 4 mm within the skin surface, and excluded ribs and lung parenchyma. The whole breast PTV (PTV_WB) excluded the boost PTV (PTV_boost). The treatment dose was prescribed with SIB as 40.5 Gy to the PTV_WB and 48.0 Gy to the PTV_boost, in 15 fractions over 3 weeks, delivering 2.7 and 3.2 Gy/fraction to each PTV. Plans were optimized for VMAT (as RapidArc) delivery, with two partial arcs in a range from the classical medial tangential beam to the posterior entrance, through the PTV side; PRO optimization algorithm was used. Plan objectives were the following as concern target coverage and homogeneity: near-to-minimum dose $D_{98\%}$ >95% for both PTVs, near-to-maximum dose $D_{2\%}$ <107% for PTV_WB (where $D_{x\%}$ is the dose delivered to at least or at most x%). Dose parameters for organs at risk were the following: ipsilateral lung should receive mean dose <10 Gy, and V_{20Gy} <10% (the volume receiving more than 20 Gy should not exceed 10%); for heart V40Gy < 3% and V_{18Gy} <5%; minimize contralateral lung and breast irradiation.

2.3. Clinical evaluation and toxicity assessment

Patient clinical evaluation was assessed during the treatment once a week. Follow-up was then scheduled at the end of the RT, at 1, 3 and 6 months after the treatment, and then every 6 months for the first 2 years. Skin toxicity was scored using RTOG/EORTC acute and late radiation morbidity score, according to CTCAE v.4. As late skin toxicity the main endpoint was the hyperpigmentation; fibrosis and teleangiectasia were also reported. Breast pain was evaluated using CTCAE v.4. Cosmetic outcomes were ranked as: excellent/good vs. fair/poor, according to the Harvard scale [22]. Two observers (a dedicated breast nurse and a radiation oncologist) always evaluated skin toxicity.

2.4. Data and statistical analysis

Toxicity and outcome data were analysed stratifying the patient population in three treatment categories: patients having received no systemic therapy (RT group), patients having received chemotherapy and not immunotherapy (CT group), patients having received immunotherapy (IT group). Statistical analysis and data correlation was performed using the SPSS software (Statistical Package for Social Science, version 21.0). Standard descriptive statistics was used to describe the data. Univariate analysis, using ANOVA (analysis of variance) statistics for correlations, and 2-tail Fisher test, were performed to investigate the individual variables. Significance value was set to 0.05.

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