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FULL PAPER

Hypofractionated radiotherapy with concomitant boost for breast cancer: a dose escalation study

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Objective: To test the maximum tolerated dose (MTD) of a concomitant boost to the tumour bed for patients at high risk of recurrence treated with whole breast radiotherapy (RT).
Methods: Patients with breast cancer with pathological stage p$T_{1\text{-}2}$ and at least one risk factor for local recurrence such as N1 disease, lymphovascular invasion, extensive intraductal component, close margins, non-hormone sensitive disease, grading G3 were enrolled. Patients were treated with hypofractionated RT to whole breast with a dose of 40.05 Gy in 15 fractions. The dose was escalated to the tumour bed through a daily concomitant boost technique at three dose levels: 48 Gy (3.2 Gy/die), 50.25 Gy(3.35 Gy/die) and 52.5 Gy (3.5 Gy/die). Dose escalation to a higher step was carried out if all patients of the lower dose had completed the treatment without dose limiting toxicity (DLT). Skin toxicity, cosmetic evaluation and quality of life was evaluated at baseline, at treatment end and at 3 and 12 months after RT end.
Results: Three patients for each dose level were enrolled. No DLT occurred. The maximum toxicity collected during RT was G2 skin toxicity in 3 (33.3%) patients, one for each dose level. No G2 toxicity at 3 and 12 months was collected. At median follow up of 21.8 months (range: 13.5 – 40.9 months), no G2 late toxicity was recorded.
Conclusion: The 3 week course of post-operative RT with dose escalation to the tumour bed to 52.5 Gy has been achieved without dose limiting toxicities and can be tested in Phase II trials.
Advances in knowledge: In our study, we tested the highest dose level to the tumour bed ever reported in studies using accelerated hypofractionation with concomitant boost in high risk patients.

INTRODUCTION

Radiotherapy (RT) after breast-conserving surgery is a standard alternative to mastectomy for most patients with Stage I and II invasive breast cancer.[1] Post-lumpectomy whole breast irradiation (WBI) is now associated with control rates of 90–95%[2,3] and improved overall survival.[1] A boost dose to the tumour bed has shown to further reduce the rate of local failure, even if without having an impact on survival.[4] Notwithstanding the benefits of RT, 15–20% of females treated with breast-conserving surgery do not undergo adjuvant treatment[5] due to the duration of conventional RT to the whole breast.

Hypofractionation, or delivery of greater than standard 1.8–2 Gy fraction sizes per day is a method for shortening overall treatment time in breast cancer and improving patients' compliance thereby leading to a greater utilization of post-operative RT with economic and logistic advantages for radiotherapy departments.

Moreover, given that breast cancer cells are more sensitive to the effects of fraction size with a α/β ratio of 4 Gy, the use of hypofractionation may be more effective than standard schedule. As a consequence of the larger fraction sizes used, total dose should be lowered to reduce normal tissue late toxicity.[6]

Four prospective randomized clinical trials have shown good results with hypofractionated schedules for WBI.[7–10] With 5–10 year follow-up, there has been similar in-breast local control between the hypofractionated and standard fractionated arms. In these studies, the role of the boost dose to tumour bed was not addressed. In fact, in the Canadian trial no patient received a boost, while in the other

three randomized trials an additional dose to tumour bed was delivered sequentially to only a percentage of patients (42–75%). Consequently, there is a lack of consistent data on how to integrate tumour bed boost to a hypofractionated regimen, and the ASTRO guidelines recommended sequential boost when hypofractionated WBI is delivered.[11]

Nevertheless, a radiation boost may be indicated in order to improve local control after whole-breast irradiation especially in subgroups of patients at greater risk of local failure after breast-conserving surgery and radiation therapy. Recognized clinical and pathological risk factors are: young age,[12] close or positive margins,[13] presence of an extensive intraductal component, absence of estrogen receptors[14] and lymphovascular invasion (LVI).[15] Some molecular subtypes are also associated with a higher rate of local failure.[16]

In these settings, a tumour bed dose escalation trial is justified by using an integrated boost to limit radiation induced side-effects. Based on the above considerations, the primary objective of this study is to test the maximum tolerated dose (MTD) of a concomitant boost to the tumour bed for patients at high risk of recurrence after having been treated with whole breast radiotherapy. The secondary objective is to evaluate the acute and late toxicity related to the treatment, the cosmetic result recorded by appropriate scales, as well as the quality of life (QoL) reported by patients.

METHODS AND MATERIALS

Eligibility

Patients with histologically proven breast cancer who have undergone conservative surgery with a pathological Stage I–II and the presence of at least three inserted clips were considered eligible. Moreover, all females enrolled should have had at least one of the following factors associated with an increased risk of local recurrence: N1 disease, LVI, extensive intraductal component, close margins (<2 mm), non-hormone-sensitive disease, grading 3.

Patients had to be older than 18 years, with at least 5 years of life expectancy, with an ECOG performance status <2 and adequate bone marrow (haemoglobin concentration >8 g dl^{-1}, white blood cell count >3000 mm^{-3}, platelet count >75,000). Patients with previous radiation treatment to the thorax, bilateral breast cancer, neoadjuvant chemotherapy, collagen diseases, pregnant or breast-feeding and male sex were excluded from the study.

The Ethics Committee of Campus Biomedico University approved the protocol. Written informed consent was obtained from each patient.

Radiotherapy technique

For setup, patients were positioned in the supine position on a breast-board with both arms raised above the head. Subsequently, 5-mm–slice–thick axial images were acquired from the lower mandible to lung bases.

Clinical target volume (CTV), planning target volume (PTV) and organs at risk (OAR) were delineated according to RTOG guidelines[17] for breast cancer. For heart contouring, the atlas by Feng et al[18] was used.

The breast CTV consisted of the breast volume excluding the major pectoral muscle, the ribs and the lung, and after shrinking the surface borders by 5 mm. This reduction accounted for partial shade and build-up effects associated with conventional breast tangent fields. The breast PTV was defined with a 7 mm margin around the CTV to account for breathing motion and treatment setup uncertainties, excluding the external part of the patient, as well as the first 5 mm of the subcutaneous tissue and the ribs.

Surgical excision cavity was delineated with the guidance of the surgical clips (minimum number 3) and all available clinical information including hematoma, seroma and other surgery-induced changes. Tumour bed CTV included surgical excision cavity plus 15 mm three-dimensional expansion excluding the major pectoral muscle, controlateral breast and 5 mm from the skin surface. Patients with a tumour bed CTV greater than 30% of breast volume were excluded. The tumour bed CTV was expanded with a margin of 7 mm to generate the boost PTV volume (tumour bed PTV), excluding when necessary the external part of the patient and the first 5 mm of the subcutaneous tissue and the ribs.

Acceptable levels of coverage for both PTV and PTV boost were as follows: at least 95% of the breast PTV should receive at least 95% of the prescribed dose; no more than 30% of the breast PTV should exceed 100% of the boost prescribed dose for the three levels; the maximal point dose outside the tumour bed should not exceed 110% of the whole breast prescribed dose. Planning constraints limited 5% of the heart volume to receive 18 Gy (mean heart dose $\leq$4 Gy) and 10% of the ipsilateral lung volume to receive <20 Gy. Isolated hot spots of more than boost prescribed dose outside of the PTV boost were not allowed. The plans were generated using "field-in-field" technique in order to meet dose-volume constraints and improve the uniformity of the dose distribution.

Radiation dose escalation

The study was designed as a monocentre early Phase I study. All patients were treated with hypofractionated RT to whole breast to a dose of 40.05 Gy in 15 fractions delivered in three-dimensional conformal radiotherapy with forward planning using a field-in-field technique. Beams of 6–15 MV energies were used.

The dose delivered to whole breast was identical to the schedule used in the UK START B[10] in the hypofractionation arm, 40 Gy in 15 fractions, 2.67 Gy per fraction over 3 weeks.

The dose escalation to the tumour bed was delivered through a daily concomitant boost technique at 3 levels of dose: 48 Gy (3.2 Gy/die), 50.25 Gy (3.35 Gy/die) and 52.5 Gy (3.5 Gy/die) for the first, second and third level respectively. The choice of the first dose level was derived from its use with a good tolerance profile

Table 1. Tumour bed dose levels (biologically effective dose values for tumour control, acute and late effects)

Level	Tumour bed dose (Gy)	BED tumour control (α/β 4 Gy)	BED acute effects (α/β 10 Gy)	BED late effects (α/β 3.4 Gy)
1	48	86.4	63.36	93.17
2	50.25	92.33	67.08	99.76
3	52.5	98.43	70.87	106.54

BED, biologically effective dose.

in the study by Formenti et al.[19] The third level of dose was biologically equivalent to that of the sequential boost-technique comprising 25 fractions of 2 Gy to the whole breast PTV followed by a boost irradiation in eight fractions, using an α/β ratio of 4 Gy for tumour response, based on the linear-quadratic cell survival model. We chose this level of dose since it was approximately the isoeffective dose delivered in 2 Gy used in the randomized trial conducted by Bartelink et al[2] which demonstrated across a large population a reduction in the incidence of ipsilateral breast tumour recurrence. The tumour control BED values were determined for each level of dose by using a α/β ratio of 4 Gy, which has been suggested for breast carcinoma. BED calculations were also performed for normal tissue adverse effects: late reacting tissues (leading to breast fibrosis, skin telangiectasia) by using a α/β ratio 3.4 Gy and acute reacting tissue (leading to erythema) by using an α/β ratio 10 Gy (Table 1).

A minimum of three patients was included for each dosage level (three additional patients if a dose limiting toxicity (DLT) Grade > 2 occurred); dose escalation to a higher step was allowed if all patients of the lower one had completed the treatment without DLT. MTD was defined as the dose level below the dose-induced DLT in at least three patients treated at a given dose level.

Patients' evaluation

A clinical evaluation of the patients was carried out before treatment, during radiotherapy, at the end of the same and at 3 and 12 months after the end of RT.

Skin toxicity was visually assessed by objective clinical exam and photographs of irradiated breast in frontal and lateral view during each visit (during treatment and during follow-up). Toxicity was scored according to NCI CTCAE (Common Terminology Criteria for Adverse Events) v. 4.02 scale.

In addition to skin toxicity, a cosmetic evaluation was performed by a radiation oncologist, an in-training physician and the patient herself according to the European Organisation for Research and Treatment of Cancer (EORTC) Cosmetic Rating System for Breast Cancer. In brief, the patient, the radiation oncologist and the in-training physician were asked to compare the treated breast with the untreated breast and grade the following items: breast size and shape, location and shape of areola/nipple, skin colour, breast oedema, the appearance of the surgical scar, telangiectasia and global cosmetic result. Items were graded on the following 4-point scale: no difference or excellent, small difference or good, moderate difference or fair, and large difference or poor.

The patients were also asked to fill in the European Organization for Research and Treatment-QoL questionnaire and breast cancer specific module (EORTC QLQ-C30 and QLQ-BR23) on QoL at each evaluation.

Statistical analysis

The primary objective was the evaluation of the MTD of concomitant boost for to the tumour bed for patients at high risk of recurrence treated with hypofractionated whole breast radiotherapy. The secondary objective was the analysis of acute toxicity, cosmetic result and patient's QoL. Statistical analysis was performed with SYSTAT, version 11.0 (SPSS, Chicago, IL).

RESULTS

Patient's characteristics

Between June and August 2014, we recruited three subsequent triplets of patients for a total of 9 patients with a median age of 61 years (range 44–65 years), whose characteristics are given in Table 2. Surgery consisted of lumpectomy and sentinel node biopsy and lymphadenectomy in five patients. The median number of nodes removed was 28 (range 15–31). Pathological stage according to AJCC TNM system, 2010 edition was Ia in 44.4%, Ib 11.1% IIa in 33.3% and IIb 11.1%. Four patients (44.4%) underwent adjuvant chemotherapy and they started radiotherapy a median of 242 days after surgery (range 194–286). In the other five patients (55.6%) radiotherapy was initiated a median of 84 days after surgery (range 83–86). All treatment plans met the planning criteria. All the patients completed treatment to the prescribed dose. All patients were considered assessable for evaluation.

Toxicity

No dose limiting toxicity Grade > 2 occurred, so we were able to reach the third level of dose without the need to recruit more than three patients per level. Acute toxicity observed is listed in Table 3. The maximum toxicity collected during RT was G2 skin toxicity in three (33.3%) patients (one for each dose level). At the end of treatment, we collected G2 skin toxicity in only one patient for the first level of dose, and not G2 skin toxicity for the second and third level of dose. No dermatitis/desquamation occurred in the boost region. We did not collect any G2 toxicity at 3 and 12 months. At median follow up of 21.8 months (range: 13.5–40.9 months) we did not record any G2 late toxicity.

Cosmetic outcome

Comparing the baseline cosmetic score with that collected at the end of the treatment, there was an improvement in the score (corresponding to a reduction of the total score) in three

Table 2. Patient's characteristics

	N(%)
Patients	9 (100%)
Age, years	
Median	61
Range	44-65
Stage	
I	5 (55.6%)
II	4 (44.4%)
Histology	
Invasive ductal	*8(88.8%)*
Invasive lobular	1 (11.2%)
ER	
Positive	9 (100%)
Negative	*0*
PR	
Positive	8 (88.8%)
Negative	1 (11.2%)
Grading	
G1	1(11.2%)
G2	4(44.4%)
G3	4(44.4%)
Cup size	
B	2(22.2%)
C	5(55.6%)
D	2(22.2%)
Chemotherapy	4(44,4%)

cases out of nine (33.3%), a stability in one case (11.1%) and a worsening in 6 (66.7%). Nevertheless, this deterioration was not statistically significant.

Moreover, patients at the beginning of treatment reported a worse cosmetic outcome (mean value 9.2) compared to that expressed by the in-training physician (mean value 8.5) and the radiation oncologist (mean value 7.7). Furthermore, at the end of the treatment patients reported a worse cosmetic outcome (mean value 10.1) compared to that expressed by the in-training physician (mean value 9.8) and the radiation oncologist (mean value 9.0). In both cases, this difference among the three operators was not statistically significant.

At a median follow-up of 18 months, we recorded an improvement of 16% from the end of RT in the mean cosmetic score for the whole patient population. These data were consistent with the improvement in the cosmetic score expressed by the in-training physician and the radiation oncologist (18.6 and 17.5, respectively). The cosmetic score recorded at 18 months was not different from the basal evaluation (p = ns).

Quality of life

The evaluation of QoL found an improvement of the score at the end of treatment compared to the initial one in seven out of nine patients (77.8%), a stability in one case (11.1%) and a worsening in 1 (11.1%). In older patients (≥62 years), the improvement in QoL is more evident, with a trend towards statistical significance (p = 0.06). Further improvement of 12% in the medium score was recorded at 18 months.

DISCUSSION

The aim of our study was to test the MTD of a concomitant boost to the tumour bed for patients at high risk of recurrence treated with whole breast radiotherapy.

In this study, we decided to escalate the total dose to the tumour bed in an early breast cancer population with high risk features (N1 disease, LVI, extensive intraductal component, close margins (<2 mm), non-hormone-sensitive disease, grading 3) from 48 to 52.5 Gy. This latter dose level is comparable in terms of isoeffective dose (α β = 4) to the 16 Gy delivered in 2 Gy fraction of the EORTC boost *vs* no boost trial. In this trial, which recently reported the 20 years update results, the cumulative incidence of ipsilateral breast tumour recurrence was 16.4% [99% confidence interval (CI) (14.1–18.8)] in the no-boost group *vs* 12.0% (9.8–14.4) in the boost group.[20] More interestingly, in young patients with a DCIS component, the boost reduced the 20 year IBTR incidence from 31% [95% CI (22–39%)] to 15% [(95% CI (8–21%)] (hazard ratio, 0.37; 95% CI (0.22–0.62); $p < 0.001$).[21]

To the best of our knowledge, we reached the highest dose level to the tumour bed ever reported in studies using accelerated hypofractionation with concomitant boost. Several Phase I–II studies investigated the use of a concomitant boost with hypofractionated whole breast radiotherapy;[19,22–28] (Tables 4 and 5) with tumour bed BED4 (α/β = 4 Gy) ranging from 74 to 96 Gy and acute effects BED10 (α/β = 10) ranging from 57.3 to 70 Gy. More than half of the patients enrolled in these studies reported acute Grade 1 skin toxicity. Overall, Grade 3 acute skin toxicity was experienced by very few patients (0–7%). Studies with a BED10 >70 Gy[24,28] reported the highest rate of Grade 2 acute toxicity (>20%). In these latter studies, however, the incidence of Grade 3 acute skin toxicity was very limited (0–1%). Interestingly, studies employing more advanced radiation technique such as intensity modulated radiation therapy or volumetric arc therapy to deliver concomitant boost[19,26,27] reported lower rates of grade ≥2 acute skin toxicity.

In our study, the maximum toxicity collected during RT was G2 skin toxicity in three (33.3%) patients (one for each dose level). These toxicity did not occur in the boost region, but in the inframammary fold in two patients and in the upper external quadrants in one patient. No patient interrupted RT due to these toxicities. At the end of treatment, only one patient had G2 toxicity which was completely resolved within 1 month. Patients experiencing toxicity had larger breast size (two cup D and one cup C).

Table 3. Toxicity description

	Toxicity (CTCAE v 4.03)			
Type (grade)	**During RT n (%)**	**End of RT n (%)**	**3 months after RT n (%)**	**1 year after RT**
Hypopigmentation				
0	9 (100)	9 (100)	7 (77.8)	9 (100)
1	0	0	2 (22.2)	0
2	0	0	0	0
3–4	0	0	0	0
Dry skin				
0	6 (66.7)	7 (77.8)	8 (88.9)	9 (100)
1	3 (33.3)	2 (22.2)	1 (11.1)	0
2	0	0	0	0
3–4	0	0	0	0
Hyperpigmentation				
0	6 (66.7)	6 (66.7)	9 (100)	6 (66.7)
1	3 (33.3)	3 (33.3)	0	3 (33.3)
2	0	0	0	0
3–4	0	0	0	0
Erythema				
0	0	0	5 (55.6)	9 (100)
1	8 (88.9)	8 (88.9)	4 (44.4)	0
2	1 (11.1)	1 (11.1)	0	0
3–4	0	0	0	0
Rash/desquamation				
0	0	0	9 (100)	9 (100)
1	7 (77.8)	8 (88.9)	0	0
2	2 (22.2)	1 (11.1)	0	0
3–4	0	0	0	0
Rash/dermatitis				
0	0	0	0	0
1	6 (66.7)	9 (100)	4 (44.4)	0
2	3 (33.3)	0	0	0
3–4	0	0	0	0
Telangiectasia				
0	9 (100)	9 (100)	9 (100)	8 (88.9)
1	0	0	0	1 (11.1)
2	0	0	0	0
3–4	0	0	0	0

RT, radiotherapy.

As we used a hypofractionated regimen with a very high dose per fraction prescribed in the highest level of dose escalation (3.5 Gy per fraction), we are aware that there is a potential of greater late toxicity. The EORTC boost *vs* no boost trial, delivering a radiation boost of 16 Gy at standard fractionation, resulted in a greater incidence of severe fibrosis (20 year incidence 5.2 *vs* 1.8% of the no boost group). Even if only few published studies of hypofractionated concomitant boost regimens reported late toxicity with follow-up longer than 2 years, the results seem nonetheless encouraging. In fact, Chada et al[22] showed no late toxicity >2 in terms of fibrosis or deterioration of cosmetics with a median follow-up of 24 months and

Table 4. Hypofractionated studies with concomitant boost: tumour bed dose

Study (ref)	Patients (*n*)	Whole breast dose	Tumour bed dose	Number of fractions	BED tumour bed (α/β = 4)
Chada[22]	160	40.5 Gy	45 Gy	15	78.8 Gy
Cante[23]	103	45 Gy	50 Gy	20	81.3 Gy
Formenti[19]	90	40.5 Gy	48 Gy	15	86.4 Gy
Freedman[24]	75	45 Gy	56 Gy	20	95.2 Gy
Morganti[25]	108	40 Gy	44 Gy	16	74.2 Gy
Raza[26]	90	40.5 Gy	48 Gy	15	86.4 Gy
Scorsetti[27]	50	40.5 Gy	48 Gy	15	86.4 Gy
Teh[28]	15	42.4 Gy	52.48	16	95.6 Gy

BED, biologically effective dose.

Table 5. Hypofractionated studies with concomitant boost: acute effects

Study (ref)	Patients (*n*)	BED acute effects (α/β = 10)	Scale	Acute toxicity (n/%)		
				G1	G2	G3
Chada[22]	160	58.5	CTCAE v.03	112 (70%)	8 (5%)	1 (7%)
Cante[23]	103	62.5	RTOG	56 (54%)	9 (9%)	2 (2%)
Formenti[19]	90	63.36	CTCAE v.03	65 (72%)	9 (10%)	2 (2%)
Freedman[24]	75	71.68	CTCAE v.03	49 (65%)	17 (23%)	0 (0%)
Morganti[25]	108	57.3	RTOG	72 (67%)	17 (16%)	1 (1%)
Raza[26]	90	63.36	RTOG	64 (71%)	1 (1%)	0 (0%)
Scorsetti[27]	50	63.36	RTOG	32 (64%)	0 (0%)	1 (2%)
Teh[28]	15	70.22	CTCAE v.03	10 (67%)	4 (27%)	1 (7%)

BED, biologically effective dose.

similarly Cante et al[23] reported no late skin and subcutaneous toxicity >Grade 2 with a follow-up of 60 months. Moreover, Raza et al[26] with a median follow-up of 61 months recorded Grade 3 teleangectasia only in one patient. With a median follow-up of 18 months we did not record any late G2 toxicity. Even if this result needs further validation with a longer follow-up period and in a larger population group, we believe that 52.5 Gy delivered in 15 fraction to the tumour bed may be safely tested in a Phase II dose trial. In fact, acute toxicity had shown to be related to late toxicity in terms of subcutaneous fibrosis and teleangectasia.[29] In addition, in our series acute toxicity occurred outside of the boost region, therefore reasonably being related to other factors such as large breast size. Moreover the boost volume was limited allowing for further reduction of the potential of toxicity.

Another secondary objective of our study was to evaluate the cosmetic result together with the QoL reported by patients. We believe that the particular setting of patients (with a good long-term prognosis) makes the cosmetic and the QoL evaluation of great interest.

To date, few studies evaluated the aesthetic results and the subsequent impact on the QoL of patients who have undergone hypofractionated regimens. When reported, the cosmetic outcomes ranged from good to excellent in most of the patients (90–100%).[30] The most commonly used scale was the Harvard criteria. As we aimed to improve consistency in the evaluation of cosmetics, we used the cosmetic self-assessment questionnaire proposed by EORTC (European Organisation for Research and Treatment of Cancer) Cosmetic Rating System for Breast Cancer.[31]

Our data are similar to that reported in the study by Freedman et al[24] which found no statistically significant differences in the pre- and post-treatment cosmetic evaluation carried out by physicians and patients themselves. In fact, after a worsening in the self-perception of cosmetics at the end of treatment in six cases (66%), probably due to acute erythema experienced during radiotherapy, at a median follow-up of 18 months, the mean cosmetic score for the whole patient population was the same as the basal evaluation.

Moreover, the cosmetic self-assessment was always worse than physicians' cosmetic evaluation; this provides an interesting data on the worst self-perception of patients, especially after diagnosis. Furthermore, residents recorded worse cosmetic assessment (higher scores) than the specialists, probably reflecting their lower experience in performing this evaluation.

Regarding QoL assessment, we found an improvement of 8% in the medium score at the end of treatment compared to the initial one, with a statistically significant trend in older patients. Further improvement of 12% in the medium score was recorded at 18 months. This is probably due to the possibility of reducing overall treatment time, improving compliance by the patient and her family, without affecting the therapeutic effectiveness of treatment.

CONCLUSIONS

The 3 week course of post-operative RT with dose escalation to the tumour bed to 52.5 Gy has been achieved without dose limiting toxicities. A Phase II study, on a larger number of patients with a longer follow-up could test the effectiveness in local control and the degree of acute and late toxicity induced by this treatment schedule.

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