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The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: A single-institution study

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ABSTRACT

Background: To evaluate the skin and heart toxicity of a concurrent adjuvant trastuzumab-radiotherapy for breast cancer (BC), especially in the case of internal mammary chain (IMC) irradiation.

Material and methods: Prospective study of 106 patients treated between 06/2003 and 03/2007 by concurrent trastuzumab-radiotherapy for non-metastatic BC. Left ventricular ejection fractions (LVEF) was assessed at baseline, before and after radiotherapy and then every 4–6 months. All toxicities were evaluated using CTCAEV3.

Results: Median age was 52 years (25–76). Chemotherapy with anthracycline was administered in 92% of patients. All patients received trastuzumab every three weeks (8 mg/kg followed by 6 mg/kg) for a median duration of 12 months (3-40). The IMC was irradiated in 83% of patients. There were: 87 grade 1, 14 grade 2 and 2 grade 3 skin reactions. There were 13 oesophagitis: 9 grade 1; 3 grade 2, and 1 grade 3. Out of 101 patients with assessments after 6 months, late telangiectasia grade 1 occurred in 5 patients, local pain grade 1 in 19 patients and grade 2 in 3 patients, fibrosis grade 1 in 16 patients. A reversible grade $\geqslant 2$ left ventricular systolic dysfunction occurred in 6 patients.

Conclusion: In this prospective study of breast cancer patients treated with trastuzumab-radiotherapy with, in most cases, anthracycline-based chemotherapy and IMC irradiation, both the rate of abnormal LVEF after concurrent trastuzumab-radiotherapy and the skin toxicity were deemed acceptable. Further follow-up is needed.

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1. Introduction

Between 15% and 25% of breast cancers (BCs) express human epidermal growth factor receptor 2 (HER-2) amplification and are at a greater risk of relapse and death.[1,2]

Trastuzumab (Herceptin®; Genentech, San Francisco, CA), a humanised monoclonal antibody against the extracellular domain of HER2, has been shown to increase the overall survival of patients with HER2-positive breast cancers both in the metastatic[3] and the adjuvant setting.[4,5] The sooner

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trastuzumab is administered, the greater its benefit, as shown by the FinHER study[6] and when concomitantly with chemotherapy.[3]

Guidelines that follow this principle request that the administration of trastuzumab should start before locoregional radiotherapy, a major component of the treatment of breast cancer that participates in enhancing not only the locoregional control of the disease but also the survival rate of patients. However, as delaying radiotherapy also appears to be detrimental[7] and because the wash-out time of trastuzumab is long (20 weeks), both treatments are usually given concurrently.

Given the radio-sensitising effect of trastuzumab on breast cancer cells,[8] concern arises regarding a potential radio-sensitisation of normal cells leading to increased toxicity in the case of a concomitant administration of both treatments. The major concern is the cardiotoxicity that has been shown to occur with trastuzumab[3,4,9] and radiotherapy[10] and that historically was an issue in the case of the irradiation of the left breast or chest-wall or of the internal mammary chain.

Limited published data exist concerning the concurrent administration of trastuzumab and detailed RT with an internal mammary chain irradiation.

The main objective of this prospective study was to evaluate the skin and heart toxicity of a concurrent adjuvant trastuzumab with radiotherapy for breast cancer, especially in the case of internal mammary chain irradiation.

2. Patients and methods

2.1. Patients

Between June 2003 and March 2007, 106 women were treated at the Institut Curie by concurrent trastuzumab-radiotherapy for clinical stage I/III, either ductal or lobular invasive breast carcinoma. Histological grading was performed according to the Nottingham Prognostic Index.[11] Positivity to estrogen receptor and progesterone receptor was determined by immuno-histochemistry using a 10% cut-off.[12] Patients with metastases or bilateral breast diseases were excluded. Therapeutic decisions were made in a multidisciplinary setting. Cosmetic results were assessed according to Harris classification.[13] Cardiac toxicity was evaluated according to the left ventricular ejection fraction (LVEF) decrease from the baseline assessment, measured by echocardiogram and/or multiple gated acquisition scan (MUGA). This assessment, along with the clinical assessment of cardiac function, was made before trastuzumab was started and subsequently at six-monthly intervals for the first 5 years and annually thereafter. Mammograms and/or ultrasound scans were performed annually. All acute and late toxicities were assessed according to the CTCAE-v3 criteria.[14]

2.2. Systemic treatment

Neoadjuvant chemotherapy was administered according to the REMAGUS 2-protocole[15]: 4 cycles of FEC100 (4 cycles of epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, 5-fluorouracil 500 mg/m^2), followed by 4 cycles of docetaxel, 100 mg/m^2; cycles repeated every 3 weeks.

Adjuvant chemotherapy consisted of 3 FEC100 followed by 3 docetaxel 100 mg/m^2.[16]

For inflammatory breast cancers that could not be operated on or for locally advanced breast cancers with involved axillary lymph node after neoadjuvant chemotherapy, 4 cycles of FUN chemotherapy (5-fluorouracil 500 mg/m^2, vinorelbine 25 mg/m^2, cycles repeated every 3 weeks) were administered concomitantly with radiotherapy.[17]

Trastuzumab was administered every 3 weeks (6 mg/kg after an initial dose of 8 mg/kg), initially associated with docetaxel, then alone for a duration of 12 months, except when patients participated in a randomised study comparing 6 months versus 12 months, the Protocol of Trastuzumab Adjuvant with Reduced Exposure (PHARE. INCA-RECF0146, EUDRACT-2006-000070-67, NCT00381901; 2006).

Hormone-therapy was given to patients with hormone-receptor positive breast cancers. It consisted of, either tamoxifen and/or LHRH analogue, in premenopausal patients or either tamoxifen or aromatase inhibitors, in post-menopausal patients.

2.3. Locoregional treatment

Local treatments, consisting of breast surgery and/or loco regional radiotherapy, were always discussed with the patient and in a multidisciplinary setting. Whenever possible, breast-conserving surgery was performed as the initial treatment. If not, the patient was offered the possibility of undergoing either neoadjuvant chemotherapy or a mastectomy. After neoadjuvant chemotherapy for non-inflammatory breast cancer, depending on the relative volumes of the residual tumour and of the breast, as assessed both clinically and by breast imaging modalities (mammography, ultrasonography and breast MRI), surgery consisted of either a tumorectomy or a modified radical mastectomy. During breast-conserving surgeries, Titanium radio-opaque clips were placed at the deep end of the resection, against the pectoral muscle to help to determine the boost volume.[18]

The only patients that did not undergo surgery were those who did not sufficiently respond to neoadjuvant chemotherapy for inflammatory breast cancers.

During surgery, all patients underwent axillary lymph node dissection of the first two levels, except those treated by primary surgery for a breast cancer of a maximal diameter of less than 15 mm, with no clinical lymph node involvement (N0), who could undergo a sentinel lymph node biopsy. Axillary lymph node dissections were performed for patients who, at the final histological evaluation, presented with either macroscopic or microscopic lymph node involvement of the sentinel lymph node.[19]

All patients treated with breast-conserving surgeries were referred to post-operative radiotherapy to the breast in either a lateral decubitus[20,21] or supine position, with an additional 16 Gy boost to the tumour bed[18] in the case of either patients younger than 60 years or those who had received neoadjuvant chemotherapy or whose tumours presented with aggressive histological features (lympho-vascular involvement and high grade or lack of hormone-receptors).

Radiotherapy was prescribed according to the IRCU (50 and later) recommendations,[22] with, for patients treated

before 2009, a clinical set-up and an *a posteriori* verification of the target volume. The dose prescription was 50 Gy to the breast (5 weekly 2-Gy fractions) whenever indicated, except for frail or elderly women who were treated with hypofractionated regimens of either 42.9 Gy (13 fractions of 3.3 Gy, 3 fractions per week) or 32.5 Gy (5 fractions of 6.5 Gy, 1 fraction per week). The breast radiotherapy constraints were a central lung distance of 20 mm and a maximum heart distance of 15 mm.[23,24]

Chest-wall electron beam radiotherapy (50 Gy in 5 weekly 2-Gy fractions)[25] was indicated if the patient had undergone neoadjuvant chemotherapy or presented with one of the following criteria: lymph node involvement, tumour size larger than 40 mm, patient younger than 40 years or the above mentioned aggressive histological features. Usually the internal mammary chain was included in the thoracic wall field and was irradiated mostly by electrons.[25]

The internal mammary chain and the supra/infra-clavicular areas (photons only with the lateral border of the field at the humeral head) were irradiated to 46 Gy in 23 daily fractions in the case of neoadjuvant chemotherapy, axillary lymph node involvement or internal breast cancers. A mixed photon and electron beam (between 6 and 12 MeV) was our technique of choice to irradiate the internal mammary chain while avoiding unnecessary irradiation of the heart, with a ratio of about 18 Gy/28 Gy between alternating photon and electron doses. For patients treated before 2009, the fields were set clinically and a verification of the IMC position was subsequently on five CT slices.[26–28] Axillary radiotherapy was indicated whenever there was more than 50% of involved axillary lymph node. Our protocol of definition and delineation of lymph node areas has been previously described.[26,28–30]

2.4. Statistical analysis

The evolution of LEVF was considered using as reference the one measured before radiotherapy. Descriptive analysis was performed using proportion (for categorical variables) and median with range (for quantitative variables). All statistics were performed using R (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org).

3. Results

3.1. Patients and treatment

Clinical features of 106 patients are summarised in Table 1.

Systemic and surgical treatments are detailed in Table 2. All patients received chemotherapy which was anthracycline-based in 92% of cases (97 patients). All patients received trastuzumab every 3 weeks (8 mg/kg followed by 6 mg/kg) for a median duration of 12 months (3–40). Hormone-therapy was given to 46 patients (43%). Breast surgery was performed in 104 patients (98%). In 2 patients (2%) radiotherapy was the only locoregional treatment (inflammatory BC).

Table 1 – Patients and tumours characteristics.

	N (106)	%
Cardiac risk factors		
Body mass index in kg/m2 (median [min–max]	23 [17–42]	
Smoker	22	21
HBP	13	12
Diabetes	1	1
Obese (body mass index >30)	12	11
Age		
⩽40 years	21	20
[40–50] years	30	28
[>50–65] years	39	37
>65 years	16	15
Age in years (median [min–max])	52 [25–76]	
Breast side		
Left	47	44
Right	59	56
Bust (cup) size		
A–B	40	35
C	25	24
D–E	13	12
MD	28	27
T stage		
T1–T2	78	74
T3–T4a–c	22	21
T4d	6	6
N stage		
N0	33	30
N1	62	59
N2	11	10
N3	5	6
Histological type of the invasive carcinoma		
Ductal	94	89
Lobular	6	6
Other	6	6
Histo-pathological grade		
2	35	33
3	68	64
MD	3	3
HR		
ER+ and/or PR+	43	40
ER– and PR–	63	60

HBP: high blood pressure; MD: missing data; HR: hormone receptors, ER: estrogen receptor, PR: progesterone receptor.

Radiotherapy was delivered, postoperatively (see details in Table 3), to the chest-wall in 48 patients (45%, 26 right and 22 left) or to the conserved breast in 58 patients (55%, 33 right and 25 left). For the latter, the positions were supine in 42 patients (72%) and lateral isocenter decubitus in 16 patients (28%). The median total dose for the chest-wall was 50 Gy (range 48–52 Gy) and 50 Gy for the breast (range 32–55 Gy). Breast complement irradiation was given in 54 out of 58 patients (86%), with a median dose of 16 Gy (range 12–27 Gy). The internal mammary chain was treated in 88 patients (83%) with a mean dose of 46 Gy (range 39–51 Gy). The supraclavicular, with or without the infraclavicular

Table 2 – Systemic treatment and surgical details.

Systemic treatment	N (106)	%
Neoadjuvant chemotherapy	40	38
Duration in months (median [min–max])	5 [1–10]	
Concurrent radio-chemotherapy	14	13
Duration in months (median [min–max])	3 [1–7]	
Adjuvant chemotherapy	78	74
Duration in months (median [min–max])	3 [1–8]	
Anthracycline either in neoadjuvant or adjuvant setting	97	92
Epirubicin total dose mg: (median [min–max])[b]	498 [460–990]	
Taxanes either in neoadjuvant or adjuvant setting	101	95
Endocrine therapy		
Aromatase inhibitors	22	21
LH-RH agonist/tamoxifen	24	23
No hormone-therapy	60	57
Trastuzumab		
Cumulative dose of trastuzumab (mg) (median [min–max])	5300 [1125–22,308]	
Total dose mg/kg (median [min–max])	90 [17–310]	
Duration in months (median [min–max])	11 [3–40]	
Breast surgery		
Breast-conserving surgery	56	53
Mastectomy	48	45
No breast surgery[a]	2	2
Axillary surgery		
ALND[c]	90	85
SLNP[d]	28	26
ALND + SLNP	14	13
No axillary surgery	2	2

[a] Two patients were treated with exclusive radio-chemotherapy.
[b] The dose of adriamycin was multiplied by 1.5 to get the equivalence in epirubicin.
[c] ALND: axillary lymph node dissection.
[d] SLNP: sentinel lymph node procedure.

Table 3 – Radiotherapy details.

	N (106)	%
Breast irradiation	58	55
Whole breast		
Total dose to the whole breast in Gy (median [min–max])	50 [32.5–55]	
Position		
Supine	42	72
Lateral	16	28
Energy		
Cobalt	23	40
XR 4MV	31	53
XR 6MV	4	7
CLD in mm for both breasts (median [min–max])[a]	10 [0–21]	
MHD in mm for left breast (median [min–max])[b]	10 [0–19]	
Breast fractionation in Gy/fraction		
⩽2 Gy	52	90
(2–5 Gy)	5	9
>5[c]	1	2
Boost		
Yes	54	93
Boost dose in Gy (median [min–max])	16 [12–27]	
Total dose (whole breast + boost) in Gy (median [min–max])	66 [32.5–77]	
Photons	37	68
Co	18	33
X4 MV	18	33
X6 MV	1	2
Electrons	17	32
<9 MeV	5	9
⩾9 MeV	12	23
Chest-wall irradiation	48	45
Total dose to the chest-wall in Gy (Median [min–max])	50 [48–52]	
Electrons	38	79
Photons	4	8
Mixed	6	13
Lymph node areas		
Internal mammary chain	88	83
left side Internal mammary chain	40	38
Supraclavicular lymph nodes	88	83
Axillary lymph nodes	20	19

RT: radiotherapy.
[a] CLD: central lung distance.
[b] MHD: maximum hearth distance.
[c] One patient was treated in the lateral isocentric position to a total dose of 32.5 Gy in 5 consecutive weeks (one fraction of 6.5 Gy per week).

lymph node region and the axillary region were irradiated respectively in 88 patients (83%) and 20 patients (19%).

3.2. Outcome

After a median follow-up of 28 months (range: 14–60 months), 105 patients (99%) were alive and 1 patient had died of cancer progression. Disease progression had occurred in 7 patients (6%) and 1 patient (1%) had developed a second cancer. Local recurrence occurred in 3 patients (3%) and distant metastases in 7 patients.

3.3. Tolerance

3.3.1. Acute tolerance (Table 4)

In the overall population, grades 2 and 3 skin reactions were seen in 16 patients (15%). Oesophageal toxicity occurred

Table 4 – Acute toxicities.

	N	%	Median dose at apparition of the maximum toxicity Gy [min–max]
Dermatitis			
Grade 1	87	82	38 [6–66]
Grade 2	14	13	38 [14–50]
Grade 3	2	2	50
Missing data	3	3	
Oesophagitis	13	12	36 [24–50]
Grade 1	9	9	36 [24–50]
Grade 2	3	3	32 [30–50]
Grade 3[a]	1	1	14
Interruption[b]	2	2	
Total RT time			
All patients time in days: median (min–max)			40 (32–71)
Breast RT time in days: median (min–max)			48 (35–71)
Chest-wall RT time in days: median (min–max)			37 (32–61)

[a] Of note, the patient with grade 3 oesophagitis had received concurrent radiochemotherapy.

[b] However RT was administered to a full prescribed dose in all patients.

during radiotherapy in 13 patients (12%): 9 patients grade 1 (8%), 3 patients grade 2 (3%), 1 patient grade 3 (2%).

3.3.2. *Cardiac tolerance*

A grade $\geqslant 2$ left ventricular systolic dysfunction occurred in 6 patients (Fig. 1): 2 asymptomatic grade 2 (i.e. LVEF 40–50%) systolic dysfunction (1 left and 1 right), 2 reversible grade 2 with grade 1 dyspnoea (1 left and 1 right), 1 reversible grade 2 with myocardial infarction and 1 reversible grade 3 with grade 1 dyspnoea (i.e. LVEF 20–40%). A myocardial infarction occurred in a 66 year-old woman, with a chronic tobacco antecedent, who underwent a left breast lumpectomy, adjuvant anthracycline-based chemotherapy, breast, internal mammary chain and supraclavicular irradiation, with a boost followed by aromatase inhibitor. Grade 3 left ventricular systolic dysfunction occurred in a 52 year old woman, with a body mass index of 40 and a long history of smoking, who underwent a left breast lumpectomy, adjuvant anthracycline-based chemotherapy and breast irradiation with a boost. Trastuzumab was stopped in 3 patients because of a decrease of left ventricular ejection fraction.

3.3.3. *Sequel and late toxicity*

Baseline cosmetic evaluation was performed at 6 months in all patients with breast-conserving treatments (58 patients) and it was found that 2 patients (3.5%) had moderate or severe deformation linked to breast surgery. After breast radiotherapy, the cosmetic result in 55 patients, with no or minor alteration at baseline, showed moderate changes in 4 (7%) and no or minor changes in 51 patients (93%).

Breast oedema was present in 4 patients (7%). No patient had either moderate or severe reduction of breast volume.

Late sequelae are reported in Table 5. Minor and moderate pain in the irradiated area was present respectively in 19 and 3 patients. Minimal fibrosis occurred in 16 patients and 5 patients developed telangiectasia in the irradiation zone. Upper limb oedema was noted in 7 patients, 6 grade 1 (increase of 5–10% compared to contralateral arm) and 1 grade 2 (10–30% increase). No ulceration was observed. One patient developed a grade 1 dyspnoea (without heart failure) before the start of radiotherapy that did not amend after radiotherapy, one a grade 1 dysphagia and 1 patient a bilateral grade 2 upper limb paresis due to a carpal syndrome channel.

4. Discussion

This is the largest mono institutional prospective series of patients treated with locoregional radiotherapy including, for most of them, internal mammary chain irradiation concurrently with concurrent trastuzumab administration. This study reports acute skin and oesophagus toxicities along with a somewhat early assessment of late and cardiac toxicities.

The percentage of patients who developed symptomatic heart failure was 4% with only 2% of patients with severe complications (one myocardial infarction and one grade 3 LVEF), which was compared to that found in the NSABP-B31 trial, where the internal mammary chain irradiation was prohibited. As expected, the left ventricular function completely recovered with longer follow-up or, in the case of the myocardial infarction, after successful angioplasty. Ewer et al. reported the reversibility of trastuzumab-related cardio toxicity of FEV, after withdrawal of trastuzumab.[30] The LVEF increased to 0.56 ± 0.11 (standard deviation) and mean time to recovery of LVEF was 1.5 months and was temporally associated with medical treatment including angiotensin-converting enzyme inhibitors and beta-blockers, in 84% of patients.

The 3-weekly administration of trastuzumab in our cohort of patients could have contributed to the good tolerance as Belkacémi et al. found only a weekly administration to be associated with LVEF decrease (that occurred in 5%, 6 out of 111 patients in their series) in multivariate analysis.[31]

The issue of whether the internal mammary chain irradiation should be prohibited in the case of a concurrent administration of trastuzumab remains controversial. The place of internal mammary chain irradiation has been addressed in two large randomised trials. A French trial of 1334 patients treated by post-mastectomy radiotherapy concluded in the absence of a 10% absolute overall survival benefit at 10 years.[32] A European trial of 4004 patients has a median follow-up of more than 7 years.[33] Data maturity for the first analysis is expected to be reached in 3–4 years. Neither trial has, so far, shown an increased risk of cardiac toxicity due to internal mammary chain irradiation. The absence of increased ischaemic heart disease in patients treated with internal mammary chain irradiation has also been reported in the Danish trials that randomised patients, with or without post-mastectomy radiotherapy, with a median follow-up over 10 years.[34]

A Canadian study examined the tolerance and cardiac toxicity in 44 patients who were irradiated concomitant with

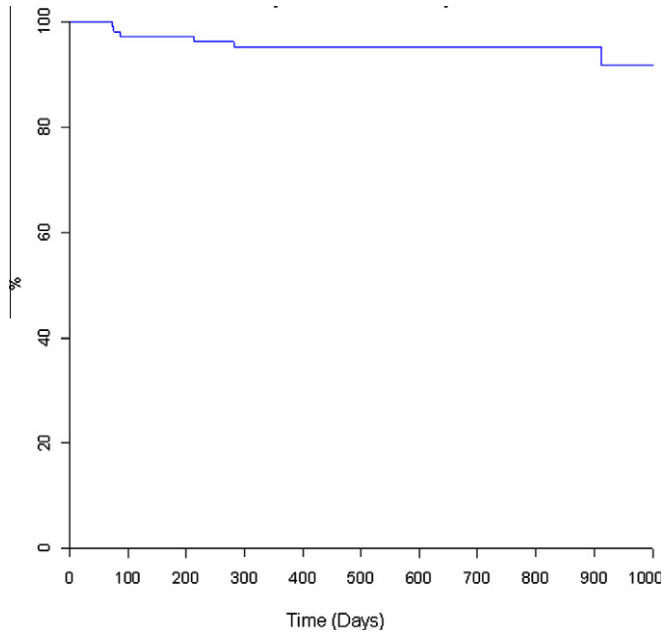

Fig. 1 – Cardiac toxicity free interval in the 106 patients treated with concurrent trastuzumab and radiotherapy.

Table 5 – Late toxicities.

Pain	All patients (106)		Breast-conserving treatment (58)		Mastectomy (48)	
	N	%	N	%	N	%
Missing data	5	5	1	2	4	8
No toxicity	79	75	44	76	35	73
Minor	19	18	11	20	8	18
Moderate	3	3	2	2	1	1
Fibrosis						
Missing data	5	4	1	2	4	8
No toxicity	85	80	44	76	41	85
Minor	16	16	13	22	3	7
Telangiectasia						
Missing data	5	4	1	2	4	8
No toxicity	96	90	55	94	41	85
Minor[a]	5	6	2	4	3	7
Lymphoedema						
Missing data	5	4	1	2	4	8
No toxicity	93	88	54	93	44	84
Minor	6	6	3	5	3	7
Moderate[b]	1	1	0	0	1	1
Late toxicity						
Total	4	4	3	5	1	2
Assessed	87	82	47	81	40	83
Missing data	19	18	11	19	8	17
No toxicity	83	78	43	74	40	83
Cardiac ischemia[c]	1	1	1	1.7	0	0
Dyspnoea	1	1	0	0	1	2
Dysphagia	1	1	1	1.7	0	0
Paresia	1	1	1	1.7	0	0

[a] In 6 out of 16 patients who developed fibrosis, concomitant chemo-radiotherapy was administered compared with 7 out of 85 patients who did not develop fibrosis ($p = 0.006$).

[b] This woman had undergone mastectomy and axillary lymph node dissection with 17 positive nodes of 22 dissected, with chest-wall, supra infra clavicular and axillar irradiation.

[c] A 66 year-old woman, with chronic tobacco antecedent; with left breast lumpectomy, adjuvant anthracycline-based chemotherapy and breast, internal mammary chain and supraclavicular irradiation with a boost followed by aromatase inhibitor.

trastuzumab out of a total of 59 patients.[35] Median absolute decrease in LVEF after radiotherapy was 4%, which was not significantly different according to side or irradiation of the internal mammary chain.

Alm El-Din et al. reported a series of 156 breast cancer patients treated with chemotherapy, trastuzumab and postoperative radiotherapy. The higher rate of cardiac events among left-sided breast cancer patients was interpreted by the authors as a suggestion that radiotherapy may be a contributing factor in the development of cardiac dysfunction.[36]

However, in the NCCTG N9831 study, 1286 patients, who received trastuzumab with (n = 908) or without (n = 378) radiotherapy, were available for analysis of clinical cardiac events. Neither the addition of radiotherapy nor the left side of BC in patients, who received radiotherapy, increased the rate of cardiac events.[42] Halyard et al. also mentioned that 41 patients (3% of the 1433 who received RT) received internal mammary chain irradiation, contrary to what was stipulated in the protocol. The rate of congestive heart failure was the same in this group compared with patients without internal mammary chain irradiation (1.4%). They concluded that, as long as cardiac sparing was verified, which was the case for all the 41 patients, the irradiation of the internal mammary chain appeared feasible. Radiotherapy techniques have been developed in our institution to minimise the dose to both the heart and the lung[20,21,25] that reflected in low values of maximum heart distance and central lung distance. Because the routine use of 3D dosimetry was introduced in 2009, dose volume histograms were, unfortunately not available. A still further step would be to better appraise which doses might be safely delivered to specific cardiac structures. It could indeed be clinically relevant to delineate the coronaries area in order to better define dose volume constraints.

LVEF assessment, despite its lack of sensitivity to slight changes in myocardial function,[37] is still the reference for cardiac toxicity. New diagnostic modalities such as cardiac-enhanced magnetic resonance imaging or biomarkers should help detect cardiac toxicity at an earlier stage.[38] In all cases, patients should be followed-up regularly for as long as possible, considering the very long time-lapse between the radiotherapy and the occurrence of cardiac toxicities and their potential toll on lives.[39]

The rate of oesophageal toxicity in this study was particularly low. A likely explanation is the choice of the internal mammary chain irradiation technique that was adapted to patients' anatomy, as previously described.[25,40] The technique of chest-wall irradiation with electrons seemed very well tolerated and made it possible to reduce the contribution of photons to the internal mammary chain with, in most cases, only 6 Gy.[25] In the case of breast-conserving treatment and the use of mixed photons and electron beams to irradiate the internal mammary chain, alternation between the two beams helped to improve the acute tolerance. The depth of the prescribed dose was always determined based on CT-scan volumes.[26]

With regard to skin toxicity, the general view of the treating physicians was that this concomitant association was not more toxic than a sequential one or even to radiotherapy alone; in the absence of trastuzumab. This is supported by the absence of grade 3 skin toxicity during RT and less than 20% of grade 2.

Belkacémi et al. reported a series of 146 patients treated by a concomitant association of trastuzumab and adjuvant radiotherapy for early stage BC. They found a grade $\geqslant$2 epidermitis in 51% of the patients associated with menopausal status and T doses.[31] Bellon et al. reported a series of 26 patients treated by concomitant radiotherapy-trastuzumab administration (81% weekly, 19% 3-weekly) for early BC.[41] The rate of grade 3 skin toxicity was 8%. Halyard et al reported a series of 2324 patients accrued in the NCCTG Phase III trial N9831 that randomised women with early stage BC with HER2 overexpression to doxorubicin and cyclophosphamide followed by weekly paclitaxel, with or without trastuzumab, that started, either during paclitaxel administration or after (3 arms).[42] Radiotherapy was allowed concurrently to T. With a median follow-up of 1.5 years, significant differences among arms in RT-associated adverse events were not identified. No significant differences existed in the incidence of skin reaction (p = 0.78) across the 3 arms in the 1460 patients who had undergone radiotherapy.

In conclusion, with a median follow-up of 28 months, the treatment by concomitant trastuzumab and radiotherapy with, in most cases, anthracycline-based chemotherapy and adapted internal mammary chain irradiation, seems to be well tolerated by breast cancer patients both in terms of acute skin toxicity and early cardiac function, as long as measures are taken to ensure that the heart is successfully spared irradiation. Longer follow-up is however essential, bearing in mind the potential late occurrence of radiation-induced toxicities, especially cardiac toxicity.

Conflict of intrest statement

None declared.

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