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Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study

Y. Belkacémi[1,2]*, J. Gligorov[3], M. Ozsahin[4,5], H. Marsiglia[6,7], B. De Lafontan[8], H. Laharie-Mineur[9], L. Aimard[10], E.-C. Antoine[11], B. Cutuli[12], M. Namer[13] & D. Azria[14]

[1]Department of Radiation Oncology, CLCC Oscar Lambret Anti-Cancer Center; [2]University of Lille II, Lille; [3]Department of Medical Oncology APHP Tenon, Cancer Est, Paris, France; [4]Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois; [5]University of Lausanne, Lausanne, Switzerland; [6]Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; [7]Florence University, Florence, Italy; [8]Department of Radiation Oncology, Institut Claudius Regaud, Toulouse; [9]Department of Radiation Oncology, Institut Bergonié, Bordeaux; [10]Clairval Clinic, Marseille; [11]Hartmann Clinic, Neuilly sur Seine; [12]Courlancy Polyclinic, Reims; [13]Department of Medical Oncology, Centre Azuréen de Cancérologie, Mougins; [14]Department of Radiation Oncology, Institut National de la Santé et de la Recherche Médicale, Montpellier, France

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Background: Trastuzumab (T) combined with chemotherapy has been recently shown to improve outcome in HER2-positive breast cancer (BC). The aim of this study was to evaluate the toxic effects of concurrent radiation therapy (RT) and T administration in the adjuvant setting.

Patients and methods: Data of 146 patients with stages II–III HER2-positive BC were recorded. Median age was 46 years. In all, 32 (23%) and 114 (77%) patients received a weekly and a 3-week T schedule, respectively. A median dose of 50 Gy was delivered after surgery. Internal mammary chain (IMC) was irradiated in 103 (71%) patients.

Results: Grade >2 dermatitis and esophagitis were noted in 51% and 12%, respectively. According to the Common Toxicity Criteria v3.0 scale and HERA (HERceptin Adjuvant) trial criteria, respectively, 10% and 6% of the patients had a grade ≥2 of left ventricular ejection fraction (LVEF) decrease after RT. Multivariate analyses revealed two independent prognostic factors: weekly T administration (for LVEF decrease) and menopausal status (for dermatitis). Higher level of T cumulative dose (>1600 mg) was only borderline of statistical significance for acute esophagitis toxicity.

Conclusion: We showed that weekly concurrent T and RT are feasible in daily clinical practice with, however, a decrease of LVEF. Cardiac volume sparing and patient selections for IMC irradiation are highly recommended. Longer follow-up is warranted to evaluate late toxic effects.

Key words: acute toxicity, breast cancer, LVEF, radiation therapy, targeted therapies, trastuzumab

introduction

The rate of breast cancers (BCs) overexpressing HER2 is ∼20% [1]. Before the targeted treatment era, HER2 BC was associated with an increasing risk of disease progression and poorer prognosis [2]. Trastuzumab (T) is a humanized recombinant mAb that binds with high affinity to the extracellular domain of the HER2 receptor [2]. Its impact on disease-free survival (DFS) and overall survival has been shown recently when given as adjuvant therapy for HER2-positive early BC [3–7]. Nevertheless, the best sequence for adjuvant T administration regarding timing of chemotherapy (CT) and radiation therapy (RT) is still unclear.

In the metastatic setting, randomized trials have indicated a synergistic effect of T and taxane combination leading to better survival compared with CT alone [8, 9]. The principal adverse event associated with T therapy among patients with prior or concurrent exposure to anthracycline was cardiac dysfunction [10].

In an experimental model of MCF-7 cell lines overexpressing HER2 and in xenograft tumors, Pietras et al. [11] reported a significant radiosensibilization of combined T and radiation exposure compared with T or radiation alone.

The risk of toxicity of combined T and RT on normal tissues has not yet been evaluated in detail. Thus, we investigated the risk of cardiac, skin, and esophagus toxic effects following concurrent administration of adjuvant T and locoregional radiotherapy in patients with HER2-positive BC.

patients and methods

This study was designed in July 2005. As there was no particular recommendation at that time for T-timing administration in France, sequential or concomitant T–radiotherapy was delivered according to each center's policy. Nine centers evaluated their patients according to

Correspondence to: Dr Y. Belkacémi, Department of Radiation Oncology, CLCC Oscar Lambret Anti-Cancer Center, 3 rue Frédéric Combemale, Lille 59020, France. Tel: +33-3-20-29-59-59; Fax: +33-3-20-29-59-72; E-mail: y-belkacemi@o-lambret.fr

a Common Toxicity Criteria (CTC) list. Each local institutional review board approved the registration.

patients

All registered patients had completely excised ductal or lobular carcinoma of the breast with HER2 overexpression or proven HER2 amplification. All patients received T and adjuvant RT.

At the time of this analysis, all patients have completed their treatment since at least 3 months. Median age was 46 years (range: 23–82 years). Ninety patients of 146 (62%) were nonmenopausal, and half of the patients were treated for left BC. The majority of the patients (98%) had grade II or III tumors, and half of them had nodal involvement (54%), or were hormone receptor positive (HR+) (53%). Patients' characteristics are detailed in Table 1.

treatment modalities

T was started before and after surgery in 71 (49%) and 75 patients (51%), respectively. In all, 78 (53%) and 68 (47%) patients had total mastectomy and conservative surgery, respectively. In all cases, T was planned for 1 year, radiotherapy was delivered concurrently with T. CT consisted of a sequential combination of anthracyclines and taxanes.

In all, 32 (23%) and 114 (77%) of the 146 patients received a weekly and a 3-weekly T schedule, respectively. The median dose of T before RT was 1600 mg (range: 0–4312 mg). Endocrine therapy was administered in 74 HR+ patients. It consisted of tamoxifen [with or without luteinizing hormone-releasing hormone (LH-RH) agonists] and aromatase inhibitors in 34 (46%) and 40 (54%) patients, respectively.

The median dose delivered to the whole breast or the chest wall was 50 Gy (range: 40–50 Gy) in 25 fractions. A 10- to 16-Gy boost in five to eight fractions was delivered to the tumor bed in 68 patients using mainly electron beams (61 of 68, 90%).

Internal mammary chain (IMC) nodes were irradiated in 103 of 146 patients (71%). The median dose was 50 Gy (range: 15–50.4 Gy) in 25 (range: 7–28) fractions delivered mainly by a mixed photon–electron technique (93 of 103, 90%). Supraclavicular nodes were irradiated in 122 of 146 patients (84%). The median dose was 46 Gy (range: 30–50 Gy) in 23 (range: 10–25) fractions delivered following mixed photon–electron beams, electrons alone, or using teletherapy unit in 77 (63%), 35 (29%), and 1 (8%) patients, respectively. Treatment modalities are detailed in Table 2.

statistical analyses

Toxicity assessment of the skin and esophagus was implemented according to the CTC v3.0 scale [12]. Cardiac toxicity was assessed according to the left ventricular ejection fraction (LVEF) decrease before and after RT completion. Acute toxicity (grade ≥2) was defined using both CTC v3.0 scale [12] and the HERA trial criteria [6] (decrease in the ejection fraction of ≥10 points from baseline to LVEF of <50% at any time).

Actuarial rates of toxic effects were calculated using the product-limit method [13]. The event was grade ≥2 toxicity at different observation times from the date of RT completion. Differences between groups were assessed using the log-rank test [14]. Multivariate analyses were implemented using the logistic regression analysis [15]. A stepwise backward procedure was used to construct a set of independent predictors of each end point. All predictors achieving a P value <0.10 were considered and sequentially removed if the P value in the multiple models was >0.05. All tests were two-sided. No P value corrections were made for multiple testing.

Table 1. Patients' characteristics (n = 146)

Parameters	n	%
Age (years)		
Median	46	–
Mean (SD)	48 (11)	–
Range	23–82	–
Menopausal status		
Menopausal	56	38
Nonmenopausal	90	62
Breast side		
Left	62	42
Right	79	54
Bilateral	5	4
Type of surgery		
TM[a]	78	53
BCS	68	47
Histology type		
Ductal carcinoma	143	98
Lobular carcinoma	3	2
Pathologic tumor size (mm)		
Median	21	–
Mean (SD)	25 (17)	–
Range[b]	0–80	–
Pathologic tumor classification		
pT0[b]	21	14
pT1	53	36
pT2	53	36
pT3–pT4	19	14
Pathologic nodal status[c]		
Node negative	67	46
Node positive[d]		
1–3 N+	55	38
≥4 N+	24	16
Grade		
Grade 1	3	2
Grade 2	52	36
Grade 3	91	62
HR status		
HR−	68	47
ER+ and/or PR+	78	53
HER2 status positive in IHC		
3+ score	134	92
2+ score	12	8

[a]Four patients had breast reconstruction.
[b]Tumor size = 0 in 21 patients who had neo-adjuvant chemotherapy +/− trastuzumab.
[c]Median number of nodes = 10 (range: 1–25).
[d]Extracapsular node involvement (n = 13).
SD, standard deviation; TM, total mastectomy; BCS, breast-conserving surgery; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptors; IHC, immunohistochemistry.

results

acute toxic effects and outcome

Acute toxic effects are detailed in Table 3. Among 135 patients who had clinical evaluation during and after the RT period, 66 (51%) developed grade ≥2 dermatitis. Grade ≥2 esophagitis was observed in 16 of 136 patients (12%). RT was suspended in three patients for 5–10 days but all of them completed the initial planned treatment.

LVEF decreased after RT ranged between 0 and 24 points (median: 6). According to the CTC v3.0 scale and HERA trial

Table 2. Treatment modalities

Groups	*n*	%
Adjuvant chemotherapy		
Total duration (months)		
Median	3.8	
Mean (SD)	4.1 (0.8)	
Trastuzumab administration modalities		
Schedule		
Weekly	32	23
3 weeks	114	77
Cumulative dose of trastuzumab (mg) (n = 137)		
<1600	65	47
≥1600	72	53
Endocrine therapy		
Type of ET (n = 74)		
TAM and/or LH-RH[a] antagonists	34	46
AI	40	54
Locoregional RT		
Dose (Gy)		
Median	50	
Mean (SD)/range	48 (2)/40–54	
Boost to the tumor bed		
Boost	68	53
No boost	78	47
IMC		
IMC RT	103	71
No IMC RT	43	29
IMC dose		
Median	50	
Mean (SD)	48 (4)	
Range	15–50.4	
SC RT		
SC RT	122	84
No SC RT	24	16
SC RT dose		
Median	46	
Mean (SD)/range	46 (3)/30–50	

[a]LH-RH antagonists administered in 24 of 90 (27%) nonmenopausal patients.
SD, standard deviation; ET, endocrine therapy; TAM, tamoxifen; LH-RH; luteinizing hormone-releasing hormone; AI, aromatase inhibitors; RT, radiation therapy; IMC RT, internal mammary chain-radiation therapy; SC, supraclavicular.

Table 3. Results of toxicity

	n	%
Skin toxicity (CTC v3.0)		
Early dermatitis (during RT; n = 143)		
Grade 0	32	22
Grade 1	53	37
Grade 2	50	35
Grade 3	8	6
Skin toxicity at any time (during or following RT; n = 135)		
≥Grade 2	66	51
<Grade 2	69	48
Esophagus toxicity (CTC v3.0)		
Early esophagitis (during RT) (n = 136)		
Grade 0	86	64
Grade 1	32	24
Grade 2	15	11
Grade 3	1	1
Esophagus toxicity at any time (during or after RT; n = 136)		
≥Grade 2	16	12
<Grade 2	120	88
RT suspended because of dermatitis or esophagitis		
RT suspended during 5–10 days		
Yes	3	2
No	88	60
NA	55	38
LVEF decrease after RT		
Decrease of LVEF (number of points)		
Median	5	
Mean (SD)	6 (5)	
Range	0–24	
Decrease of LVEF		
Defined by CTC v3.0 scale[a] (n = 92)	9	10
Defined following HERA trial criteria[b] (n = 111)	6	5

[a]CTC v3.0—grade 1: ejection fraction <60%–50%; grade 2: ejection fraction <50%–40%.
[b]HERA trial criteria: decrease in LVEF defined as a decrease in the ejection fraction of ≥10 points from baseline to an LVEF of <50% at any time.
CTC, Common Toxicity Criteria; NA, not available; RT, radiation therapy; LVEF, left ventricular ejection fraction; SD, standard deviation.

criteria, 9 of 92 patients (10%) and 6 of 111 patients (6%), respectively, had a grade ≥2 of LVEF decrease.

After a median follow-up of 16 months (range: 4–30 months), all patients were alive. Five of 146 (3%) developed distant metastases [brain (n = 2) and liver (n = 3)]. None of the patients had local or locoregional recurrence or contralateral BC.

univariate and multivariate analyses

Univariate analyses are shown in Tables 4 and 5. In terms of skin acute toxicity, 38% of the nonmenopausal patients developed grade ≥2 dermatitis versus 65% of the menopausal patients (P = 0.002). There was a trend for statistical significance between patients younger than 46 years compared with those 46 years or older (56% versus 40%; P = 0.063). In patients who received a cumulative dose of T ≥1600 mg and concurrent RT including IMC, grade ≥2 esophagitis was higher (17%) than those who received <1600 mg of T (6%) with border statistical difference (P = 0.05). A higher rate was also observed after total mastectomy compared with conservative surgery; however, the limit of statistical significance was not reached (P = 0.08). In terms of LVEF decrease after RT, either using CTC v3.0 scale or HERA criteria, we found a significant impact of menopausal status (P = 0.0006 and 0.001, respectively), age (P = 0.004 and 0.001, respectively), and weekly T schedule (P = 0.0018 and 0.005, respectively).

Table 4. Univariate analyses of early cardiac, esophagus, and skin toxic effects after RT

Parameters	Decrease of LVEF following HERA trial criteria[a]			Decrease of LVEF ≥grade 2 (CTC v3.0 scale)[b]		
	n = 111	%	*P* value	*n* = 112	%	*P* value
Age (years)						
>46	6/53	10	0.004	8/59	14	0.001
≤46	0/58	0		1/53	2	
Menopausal status						
Menopausal	6/44	5	0.0006	8/45	18	0.001
Nonmenopausal	0/67	0		1/67	1	
Breast side						
Left	1/42	2	0.24	2/43	5	0.28
Right	5/69	7		7/69	10	
Type of surgery						
TM	5/63	8	0.15	6/63	10	0.5
BCS	1/48	2		3/49	6	
Neo-adjuvant CT						
Administered	2/55	4	0.40	4/56	7	0.72
Not administered	4/56	7		5/56	9	
Adjuvant CT						
Administered	4/56	7	0.40	5/56	9	0.72
Not administered	2/55	4		4/56	7	
Total duration of CT (months)						
≥3	3/52	5	0.87	4/56	7	0.60
<3	3/59	6		5/56	9	
Type of CT						
AT	2/47	4	0.64	3/48	6	0.54
Other combinations	4/64	6		6/64	9	
Trastuzumab schedule						
Weekly	5/27	19	0.0018	6/28	21	0.005
3 weeks	1/82	1		3/84	3	
Endocrine therapy						
AI	4/31	13	0.04	5/32	16	0.07
TAM +/− LH-RH analogs	2/80	2		4/80	5	
Internal mammary chain						
RT	4/75	5	0.96	7/76	9	0.49
No RT	2/36	5		2/36	5	
Supraclavicular						
RT	5/94	5	0.92	8/95	8	0.71
No RT	1/17	6		1/17	6	
Cumulative dose of trastuzumab before RT (mg)						
<1600	1/47	2	0.12	3/47	6	0.46
≥1600	5/57	10		6/58	10	

[a]HERA trial criteria: decrease in LVEF defined as a decrease in the ejection fraction of ≥10 points from baseline to LVEF of <50% at any time.
[b]CTC v3.0—grade 1: ejection fraction <60%–50%; grade 2: ejection fraction <50%–40%.
LVEF, left ventricular ejection fraction; CTC, Common Toxicity Criteria; TM; total mastectomy; BCS: breast-conserving surgery; CT: chemotherapy; AT: anthracyclines and taxanes; AI, aromatase inhibitors; TAM, tamoxifen; LH-RH, luteinizing hormone-releasing hormone; RT: radiation therapy.

Table 5. Univariate analyses of skin and esophageal toxic effects during and 3 months following RT

Parameters	Skin acute toxicity grade ≥2 (CTC v3.0 scale)			Esophagitis grade ≥2 (CTC v3.0 scale)		
	n = 135	%	*P* value	*n* = 136	%	*P* value
Age (years)						
>46	24/60	40	0.063	7/61	9	0.33
≤46	42/75	56		9/75	15	
Menopausal status						
Menopausal	34/52	65	0.002	5/50	10	0.62
Nonmenopausal	32/83	38		11/86	13	
Breast side						
Left	23/55	42	0.17	6/60	10	0.56
Right	43/80	54		10/76	13	
Type of surgery						
TM	34/70	49	0.93	12/75	16	0.08
CS	32/65	49		4/61	7	
Neo-adjuvant CT						
Administered	33/67	49	0.93	10/69	14	0.31
Not administered	33/68	49		6/67	9	
Adjuvant CT						
Administered	33/67	49	0.93	6/67	9	0.31
Not administered	33/68	49		10/69	14	
Total duration of CT (months)						
≥3	30/63	48	0.78	8/59	14	0.57
<3	36/72	50		8/77	10	
Type of CT						
AT	26/58	44	0.41	8/63	13	0.75
Other combinations	40/77	52		8/73	11	
Trastuzumab schedule						
Weekly	14/29	48	0.86	2/30	7	0.26
Every 3 weeks	51/102	50		14/102	13	
Trastuzumab–RT combination						
Weekly	13/28	46	0.37	2/31	6	0.14
3WT-RT	42/90	46		14/96	14	
3WT after RT completion	11/17	64		0/9	0	
Endocrine therapy						
AI	19/34	56	0.34	4/36	11	0.88
TAM +/− LH-RH analogs	47/101	46		12/100	12	
Internal mammary chain						
RT	46/95	48	0.86	13/93	14	0.21
No RT	20/40	50		3/43	7	
Supraclavicular						
RT	56/113	49	0.72	15/113	13	0.17
No RT	10/22	45		1/23	4	
Cumulative dose of trastuzumab before RT (mg)						
<1600	28/59	47	0.89	4/64	6	0.05
≥1600	31/67	46		12/71	17	

CTC, Common Toxicity Criteria; TM, total mastectomy; CS, conservative surgery; CT, chemotherapy; AT, anthracyclines and taxanes; WT, weeks-trastuzumab; RT, radiation therapy; AI, aromatase inhibitors; TAM, tamoxifen; LH-RH; luteinizing hormone-releasing hormone.

Multivariate analysis revealed three unfavorable prognostic factors: weekly T administration (for the risk of LVEF decrease; $P = 0.004$ and 0.04, according to HERA and CTC v3.0 criteria, respectively), menopausal status (for grade >2 dermatitis; $P = 0.002$). The limit of statistical significance was only borderline ($P = 0.05$) for the impact of higher T cumulative dose on esophagitis.

Table 6. Multivariate analyses

Factors	Cardiac toxicity evaluation by LVEF decrease	
	LVEF decrease: HERA trial criteria[a]	≥Grade 2 decrease of LVEF (CTC v3.0 scale)[b]
Weekly trastuzumab administration	0.004	0.04
	Esophagitis grade ≥2 (CTC v3.0 scale)	
Cumulative dose of trastuzumab before RT	0.05	
	Dermatitis grade ≥2 (CTC v3.0 scale)	
Postmenopausal status	0.002	

[a]HERA trial criteria: decrease in LVEF defined as a decrease in the ejection fraction of ≥10 points from baseline to LVEF of <50% at any time.
[b]CTC v3.0—grade 1: ejection fraction <60%–50%; grade 2: ejection fraction <50%–40%.
LVEF, left ventricular ejection fraction; CTC, Common Toxicity Criteria; RT, radiation therapy.

discussion

This study was undertaken to examine whether there was an association between the use of T concurrently with RT for HER2-overexpressing BC patients in the adjuvant setting.

In the North American [3] and HERA [4, 5] phase III trials, using 1-year T schedule, the absolute DFS benefit was 12% at 3 years and 18% at 4 years, respectively. The HERA trial has recently reported a benefit of 2.7% in overall survival in patients treated by T in adjuvant setting [5]. In FinHer trial [6] with only a 9-week administration of T, the DFS benefit was 42% at 38 months. This increase of survival was associated with acceptable toxicity in particular cardiac toxicity, which was mostly reversible. Conversely, the best sequence regarding timing of RT could not be determined from these trials. Thus, it remains unclear whether concurrent administration of T and RT could alter normal cardiac, skin, and oesophageal tissues. Even if these acute reactions could be reversible, their impact on late sequelae is still not predictable.

Pietras et al. [11] have indicated a synergistic effect of T and ionizing radiation in experimental models. They showed in an *in vitro* model of MCF-7 HER2-positive cells a significant inhibition of DNA repair after concomitant X-ray and T exposure compared with T or irradiation alone. Their results were confirmed *in vivo* in xenografts using MCF-7 HER2-positive cells.

In humans, the synergistic antitumor effect of T in combination with RT has been investigated recently in HER2-positive high-risk ($n = 15$) and chemoresistant ($n = 7$) BC [16]. The schedule consisted of hypofractionated and accelerated irradiation combined to 4 mg/kg every 2 weeks of T. CT consisted of doxorubicin (25 mg/m^2 every 2 weeks) or docetaxel (40 mg/m^2 every 2 weeks). With the addition of a cytoprotectant (Amifostine, Ethyol®; Schering Plough Laboratories), this schedule was well tolerated. After 3–26 months of follow-up there was no recurrence. A complete response was observed in 5 of 7 patients with locally advanced or chemoresistant disease.

The concern of our study was the potential synergistic effect of concurrent T–RT on normal tissues involved in the radiation field.

The overall incidence of grade 2 or more acute skin reactions was 51%. The follow-up in our study remains short and render impossible to predict the outcome of skin reactions and particularly the probability of late breast fibrosis. In the Dana Farber experience [17], using a weekly concurrent T (2 mg/m^2; $n = 21$) or a 3-weekly schedule (6 mg/m^2; $n = 5$), the grades 2 and 3 skin toxicity rates were 48% and 8%, respectively. The median follow-up period of 26 months is still short to allow relevant evaluation of late skin sequelea. In this series two patients (8%) developed interstitial pneumonitis. In our experience, among the patients who received supraclavicular RT (84%), none developed lung toxicity clinically after a 16-month median follow-up period. In addition, it is important to point out that none of these preliminary reports have taken into account age and the breast volume variation for skin toxicity evaluation.

Halyard et al. [18] reported a retrospective comparison of irradiated ($n = 908$) versus nonirradiated patients ($n = 308$) from the North Central Cancer Treatment Group phase III trial. After an 18-month median follow-up, concurrent T and RT administration did not increase skin toxicity ($P = 0.78$), interstitial pneumonitis ($P = 0.78$), dyspnea ($P = 0.87$), or esophagitis ($P = 0.26$). The results regarding esophagus and cardiac toxic effects have to be interpreted cautiously as the authors reported that among the 41 patients (3%) who had IMC irradiation the heart was shielded using blocks. In such cases, the pertinence of esophagus and cardiac toxicity analysis has to be questioned regarding the very low doses delivered to these tissues.

In the current report and according to the widely known impact of cumulative dose of anthracyclines on cardiac toxicity, we analyzed the influence of cumulative dose of T on acute toxic effects. In contrast to the anthracyclines data on heart and skin radiosensibilization, cumulative dose of T did not modify radiation-induced acute toxic effects of these tissues. Among 71% of the patients who received a median dose of 50 Gy to the IMC, the rate of grade 2 or more esophagitis was 12% during RT but remained reversible in the majority of the cases (11%) at 3 months after treatment. This has to be interpreted cautiously as there are no available data in the literature supporting this finding for the moment. In addition, the limit of statistical significance was not reached in the multivariate analysis for T cumulative dose impact on esophagitis (Table 6). Further studies and long-term follow-up are warranted to evaluate late sequelea. In the meta-analysis, the risk of secondary esophagus malignancy after BC treatment before T era was significantly increased by RT (relative risk = 2.06; $P = 0.05$) [19].

There are two options to reduce the risk of radiation-induced toxicity of the mediastinal organs. The first option may consist in a high selection of patients who will really benefit from IMC irradiation, such as patients having total mastectomy and significant axillary node involvement (≥4 nodes) [20]. In a comparison between IMC irradiation practice in Europe and in the United States, Taghian et al. [21] reported a significant difference between the French and

American practice for both subgroups of patients who had total mastectomy for intermediate-risk (1–3 nodes; 59% versus 15%) or high-risk (≥4 nodes; 64% versus 24%) BC. This difference in practice should be taken into account for interpreting results in future studies involving patients receiving T and RT.

The second option may consist in the use of intensity-modulated radiation therapy (IMRT) and gating, which could allow a highly conformal dose distribution to the breast (or chest wall) and elective nodes. In the William Beaumont Hospital experience on 25 patients, the mean cardiac volume receiving 30 Gy was decreased from 2.6% to 0.6% using IMRT and gating compared with other techniques. In this series, the cardiac volume was totally excluded from the irradiation field in 15 of 25 patients [22]. Furthermore, another report from the same group has recently indicated a significant dose reduction via active breathing control during irradiation for left-sided BC. This was demonstrated using image fusion from magnetic resonance imaging and computed tomography scans [23].

Even if no difference in terms of cardiac toxicity was observed between patients treated for left or right side [24], irradiated heart volume, previous cumulative dose of anthracyclines, and T administration are highly suspected to be involved in the cardiac injury. In addition, it is impossible to predict whether the reversible decrease of LVEF during T therapy will impact the late cardiac toxicity in the context-additive effect of anthracyclines and RT. In the metastatic setting, a recent report from MD Anderson [25] showed that the two main prognostic factors for long-term cardiac tolerability of T were baseline LVEF and time from last anthracycline administration. In our study, the analyses took into account the last LVEF value measured before RT as the reference value. This baseline value was compared with the lowest value observed at any time of follow-up following RT.

The recent retrospective data analysis of the INTERGROUP randomized trial [18] did not show any difference according to the breast side following T and RT. However, the number of patients who received an IMC RT was low and the follow-up in this report is still too short to conclude. In a recent report with longer follow-up after RT alone, Harris et al. [26] reported an increased cumulative hazard risk of cardiac death in patients treated for right BC (2.9% at 15 years and 3.6% at 20 years) compared with the left side (4.4% at 15 years and 6.4% at 20 years). In addition, myocardial infarction rate was significantly higher in left-side BC patients (15% versus 5%; $P = 0.006$). In another recent report, the risk of myocardial infraction following RT for BC was related to anatomic sites of RT, such as left breast, anterior left breast boost field, and anterior IMC field [27]. Indeed, when IMC RT is delivered using only anterior beam's photons, the cardiac dose may increase significantly which can lead to an increased risk of toxicity.

In the present study, the decrease of LVEF according to HERA and CTC v3.0 criteria have evaluated only acute cardiac toxicity after a 16-month median follow-up. Multivariate analysis using both criteria showed that weekly T schedule was the only unfavorable factor for LVEF decrease. In our study, 23% and 77% of the patients had weekly and a 3-week schedule, respectively. The timing and extent of LVEF reduction after RT alone, however, have to be discussed. Following left breast RT alone or combined to doxorubicin, the cardiac perfusion defects detected using single-photon emission computed tomography are not associated with changes in regional wall motion or LVEF. To date, there is no report on evaluating this issue after combined T–RT [28, 29].

Suspending T during RT may not be useful to prevent cardiac toxicity. Indeed, in practice, such suspension may be useless because of the half-life of T (∼4–6 weeks). Besides, there is a pharmacological similarity between daily and 3-weekly administration of T [30]. In HER2-overexpressing BC, however, the impact of late outset and/or suspension of T for 5–7 weeks of irradiation is still unknown. In the case of concomitant administration of T and RT, the issue lies in the potential interaction between T set on cardiac tissue structures and ionizing radiation. Whereas for anthracyclines and ionizing radiation the physiopathology is on the basis of the production of free radicals, cell events are less known for T. Indeed, one limit of preclinical studies is that the antibody's humanized variable part is unable to recognize and thus bind to HER2 receptor in nonsyngeneic animal models. Moreover, in humans, HER2 expression on myocardiac cells is low. On myocardiac cells, however, we noticed HER2/HER4 heterodimers showing the dimerization of HER receptors as well as the involvement of mitogen-activated protein kinase/extracellular signal-regulated kinase and AKT pathways [31, 32]. Such pathways may also be involved in explaining doxorubicin/T-induced additive toxicity on myocardiac cells. The doxorubicin-induced apoptotic phenomena might increase with the addition of T, inhibiting AKT and extracellular signal-regulated kinase signal transduction [33]. In addition, interaction between ionizing radiation and these pathways is known.

conclusion

To our knowledge this is the first study evaluating acute toxicity of concurrent administration of T and RT. We found that weekly concurrent T and RT decreased LVEF. The acute skin and esophagus toxic effects have been resolved at 3 months following RT. Longer follow-up is warranted to evaluate whether acute reversible reactions could be predictors of significant sequelea, in particular cardiac late toxicity in the setting of anthracycline administration and aromatase inhibitors era.

At the moment, it is recommended to balance the role of each therapeutic agent and their potential toxic effects when used concurrently. It is important to spare the maximum of heart volume during RT and select the patients who will really benefit from IMC irradiation.

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