Received:
27 November 2014

Revised:
27 January 2015

Accepted:
2 February 2015

doi: 10.1259/bjr.20140800

Cite this article as:

Pernin V, Belin L, Cottu P, Bontemps P, Lemanski C, De La Lande B, et al. Late toxicities and outcomes of adjuvant radiotherapy combined with concurrent bevacizumab in patients with triple-negative non-metastatic breast cancer. Br J Radiol 2015;88:20140800.

FULL PAPER

Late toxicities and outcomes of adjuvant radiotherapy combined with concurrent bevacizumab in patients with triple-negative non-metastatic breast cancer

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Objective: To evaluate the safety of the concurrent combination of bevacizumab with adjuvant radiotherapy (B-RT) in breast cancer (BC).

Methods: Multicentre, prospective study, of the toxicity of adjuvant radiotherapy (RT) alone or B-RT in patients with non-metastatic BC enrolled in randomized Phase 3 BEATRICE trial. Early and late toxicities were assessed by the Common Terminology Criteria for Adverse Events v. 3.0 during and 12 months after the completion of RT.

Results: From 2007 to 2012, 39 females received adjuvant B-RT and 45 received adjuvant RT alone. Median follow-up was 21.5 months. All patients had triple-negative non-metastatic BC and received adjuvant chemotherapy followed by RT. 90% of the 39 females treated by concurrent B-RT received whole breast irradiation (WBI) with a boost and 4 (10%) received post-mastectomy RT. Lymph node RT

was delivered in 49% of the females with internal mammary chain irradiation. The mean duration of bevacizumab was 11.7 months. 38 (84%) females treated by RT alone received WBI with a boost and 16% of the females received post-mastectomy RT. Lymph node RT was delivered in 47% of the females with internal mammary chain RT in 31%. Grade 3 acute dermatitis was observed in 9% of patients receiving B-RT and 5% of patients receiving RT alone with no significant difference. 1 year after the completion of RT, the most common late grade 1–2 toxicities in the B-RT group were pain (18%), fibrosis (8%) and telangiectasia (5%).

Conclusion: The concurrent bevacizumab with locoregional RT is associated with acceptable early and late 1-year toxicities in patients with BC.

Advances in knowledge: The largest series of this association.

Following the encouraging results of bevacizumab in combination with chemotherapy in many metastatic tumour settings, bevacizumab has been developed in the adjuvant setting in breast cancer (BC), especially in the context of the BEATRICE trial. The BEATRICE trial (NCT00528567) is a Phase 3 trial designed to evaluate the efficacy and safety of the combination of bevacizumab and chemotherapy in the adjuvant setting in patients with

triple-negative BC.¹ Patients included in the trial were randomized to either the standard treatment arm comprising standard adjuvant chemotherapy alone or followed by radiotherapy (RT) according to the standard practice of each centre, or the experimental arm comprising standard chemotherapy combined with bevacizumab either alone or followed by RT. BEATRICE randomization was stratified according to the type of surgery, lymph node status and

chemotherapy. The dose of bevacizumab administered had to correspond to the equivalent of 5 mg kg^{-1} per week, and the duration of bevacizumab therapy was 1 year. The primary objective of this study was to determine the disease-free survival in each of the two arms. Patient inclusion has ended, and the trial is maturing and waiting for follow-up results. The BEATRICE trial study plan is presented in Figure 1. During this trial, patients included in the experimental arm received bevacizumab with locoregional RT of the breast. However, the long-term effects of this concurrent combination on the skin, healthy breast tissues, the lung and the heart included in breast and lymph node irradiation volumes are unknown. The only available data are derived from the retrospective comparative study by Goyal *et al*² based on 14 patients who received concurrent bevacizumab and RT (B-RT) and matched with controls. The results of this study demonstrated the good safety of concurrent B-RT with no acute locoregional toxicity $\geq$ grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 3 scale. However, the study by Goyal *et al* only reported the acute toxicities of the combination, and no data on late toxicities are available at the present time. The objectives of this study were to evaluate in the cohort of patients included in the BEATRICE trial treated by concurrent B-RT and in the cohort of patients treated by RT alone:

- (1) acute locoregional toxicity
- (2) the cosmetic result for patients managed by breast-conserving therapy
- (3) late locoregional toxicity.

METHODS AND MATERIALS

84 patients who had participated in the BEATRICE trial were included in this French multicentre cohort study between October 2007 and November 2012. The cohort without bevacizumab and the cohort with bevacizumab comprised 45 and 39 patients, respectively. Evaluation 1 year after the completion of RT was available for all patients, and acute and late locoregional toxicities of RT could be compared between the 45 patients who received adjuvant RT alone and the 39 patients who received the concurrent B-RT combination.

The baseline evaluation comprised recording of medical history, World Health Organization performance status, physical examination and a laboratory work-up. Patients were evaluated once a week during RT, 4 weeks after the completion of RT then every 3–6 months thereafter. Data concerning the locoregional toxicity of treatment included acute radiation dermatitis, acute oesophagitis, pain, radiation fibrosis, lymphoedema of the arm, ulcerations, telangiectasia, dysphagia, dyspnoea, plexitis, pericarditis and myocardial infarction.

Acute toxicity was graded according to the CTCAE v. 3 scale. According to this system, acute toxicity is graded from grade 1 (minor toxicity) to grade 5 (death). In this study, acute toxicities were considered to be severe for grades ≥ 3 . The cosmetic appearance of the conservatively treated breast was evaluated by the classification of cosmetic results described by Harris *et al*.³

Qualitative variables were described by frequencies, and quantitative variables were described by their means and/or medians with variances and/or range. The χ^2 test and Student's *t*-test were used for comparisons. When the conditions of application of these tests were not satisfied, non-parametric Fisher or Wilcoxon tests were preferred. The Cochran–Armitage test for trend was performed in order to compare ordinal qualitative variables between the two groups. Analyses were performed with R v. 2.13.2 software (www.csm.ornl.gov/esh/statoed).

RESULTS

In this ancillary study derived from the BEATRICE randomized trial, 39 patients received bevacizumab concurrently with adjuvant RT and 45 patients received adjuvant RT without concurrent bevacizumab.

Patient characteristics

In the bevacizumab arm, 67% of patients were post-menopausal. The majority of patients (62%) were between the ages of 40 and 60 years. The left breast was affected in 56% of cases. Clinical stages of BC were distributed as follows: 49% for Stage I and 51% for Stage II. The most common histological type was invasive ductal carcinoma (87% of cases), histological grade was generally high (grade III in 85% of cases), and all patients had triple-negative BC.

In the arm without concurrent bevacizumab, 49% of patients were post-menopausal. The majority of patients were between the ages of 40 and 60 years. The left breast was affected in 53% of cases. Clinical stages of BC were distributed as follows: 44% for Stage I, 47% for Stage II and 7% for Stage III. The most common histological type was invasive ductal carcinoma; histological grade was generally high (grade III in 91% of cases); and all patients had triple-negative BC. No significant differences over these clinical and histological characteristics were observed between the two arms. The patients' characteristics are given in Table 1.

Figure 1. BEATRICE trial study plan.

Table 1. Patient characteristics

Patient characteristics	Bevacizumab + RT, <i>n</i> (%)	RT alone, <i>n</i> (%)	<i>p</i> -value
Menopause	26 (67%)	22 (49%)	0.1
Cardiovascular risk factors			NS
Obesity (body mass index >30 kg m ⁻²)	5 (13%)	10 (22%)	
Hypertension	4 (10%)	5 (11%)	
Smoking	4 (10%)	7 (16%)	
Diabetes	1 (3%)	2 (4%)	
Deep arterial or venous thrombosis	0	0	
Age (years)			NS
<40	9 (23%)	12 (27%)	
40–60	24 (62%)	26 (58%)	
61–70	6 (15%)	5 (11%)	
>70	0	2 (4%)	
Side			NS
Left breast	22 (56%)	24 (53%)	
Right breast	17 (44%)	21 (47%)	
Histology			NS
Invasive ductal	34 (87%)	43 (96%)	
Invasive lobular	2 (5%)	0	
Others	3 (8%)	2 (4%)	
Clinical T stage			NS
T0	2 (5%)	0	
T1	24 (62%)	25 (56%)	
T2	13 (33%)	17 (38%)	
T3	0	3 (7%)	
T4	0	0	
Tx	0	0	
Clinical N stage			
N0	29 (74%)	32 (71%)	NS
N1	10 (26%)	10 (22%)	
N2	0	2 (4%)	
N3	0	0	
Nx	0	0	
Missing data	0	1 (2%)	
Union for International Cancer Control stage			NS
Stage I	19 (49%)	20 (44%)	
Stage IIA	17 (44%)	14 (31%)	
Stage IIB	3 (8%)	7 (16%)	
Stage IIIA	0	3 (7%)	
Stage IIIB	0	0	
Missing data	0	1 (2%)	

(Continued)

Table 1. (Continued)

Patient characteristics	Bevacizumab + RT, <i>n</i> (%)	RT alone, <i>n</i> (%)	<i>p</i> -value
Histological grade			NS
I	0	1 (2%)	
II	6 (15%)	2 (4%)	
III	33 (85%)	41 (91%)	
Missing data	0	1 (2%)	
HR status			NS
HR+	0	0	
HR–	39 (100%)	45 (100%)	
HER2 overexpression			NS
Overexpression	0	0	
No overexpression	39 (100%)	45 (100%)	
Triple-negative breast cancer	39 (100%)	45 (100%)	NS

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NS, not significant; RT, radiotherapy.

Systemic treatment characteristics

All patients received adjuvant chemotherapy according to the BEATRICE protocol.

In the bevacizumab arm, the majority of patients (87%) received anthracycline-based sequential combination chemotherapy followed by taxane-based chemotherapy concurrently with bevacizumab. The median duration of bevacizumab therapy was 11.7 months.

In the arm without concurrent bevacizumab, the majority of patients (88%) received anthracycline-based sequential combination chemotherapy followed by taxane-based chemotherapy (Table 2).

Surgery characteristics

In the bevacizumab arm, surgery consisted of total mastectomy for 10% of patients and breast-conserving surgery for 90% of patients. The sentinel lymph node technique was used in 20 (51%) patients and axillary lymph node dissection was performed in 72% of cases.

In the arm without concurrent bevacizumab, surgery consisted of total mastectomy for 16% of patients and breast-conserving surgery for 84% of patients. The sentinel lymph node technique was used in 21 (47%) patients and axillary lymph node dissection was performed in 62% of cases. No significant difference over the treatment characteristics was observed between the two arms (Table 2).

Radiotherapy characteristics

Among the 39 patients who received concurrent B-RT, 35 (90%) received RT to the breast alone at a median dose of 50 Gy plus a boost to the tumour bed at a median dose of 16 Gy, and 4 (10%) patients received chest wall RT at a median dose of 50 Gy. RT of the draining lymph nodes was performed in 19 (49%) patients; this RT concerned the supraclavicular nodes in 44% of

cases and the internal mammary nodes in 31% of cases. The median duration of RT was 49 days for breast RT with a boost to the tumour bed $\pm$ lymph nodes and 38 days for RT of the chest wall $\pm$ lymph nodes. The median interval between surgery and RT was 184 days.

Among the 45 patients who did not receive concurrent bevacizumab with RT, 38 (84%) received RT to the breast alone at a median dose of 50 Gy plus a boost to the tumour bed at a median dose of 16 Gy, and 7 (16%) patients received chest wall RT at a median dose of 50 Gy. RT of the draining lymph nodes was performed in 21 (47%) patients; this RT concerned the supraclavicular nodes in 44% of cases and the internal mammary nodes in 31% of cases. The median duration of RT was 49 days for breast RT with a boost to the tumour bed $\pm$ lymph nodes and 38 days for RT of the chest wall $\pm$ lymph nodes. The median interval between surgery and RT was 186 days.

No significant difference was observed between the two arms (Table 2).

Higher acute toxicities (radiation dermatitis and oesophagitis) during or after radiotherapy (less than 6 months)

Acute radiation dermatitis was evaluated on 35 (90%) patients and was revealed in 30 (86%) patients in the bevacizumab arm; the results are shown in Table 3.

All patients were evaluated for oesophagitis. Only one grade 2 acute oesophagitis was observed in the bevacizumab arm, and no acute oesophagitis was described for patients in the arm without concurrent bevacizumab (Table 3).

Cosmetic results 1 year after the completion of radiotherapy

Cosmetic assessment was performed for 25 (64%) patients in the bevacizumab arm. Cosmetic results were grade 0 for

Table 2. Treatment modalities

Radiotherapy characteristics	Bevacizumab + RT, <i>n</i> (%)	RT alone, <i>n</i> (%)	<i>p</i> -value
Systemic treatment characteristics			
Adjuvant chemotherapy	39 (100%)	45 (100%)	NS
Adjuvant chemotherapy protocols			NS
Anthracycline-based chemotherapy	2 (5%)	3 (7%)	
Taxane-based chemotherapy	3 (8%)	2 (4%)	
Sequential combination	34 (87%)	40 (89%)	
Bevacizumab			
Median dose (mg)	15,000 (3330–28,080)		
Median duration (months)	11.7 (2.1–12.6)		
Surgery characteristics			
Type of surgery			NS
Conservative surgery	35 (90%)	38 (84%)	
Mastectomy	4 (10%)	7 (16%)	
Conservative surgery then mastectomy	0	0	
No surgery	0	0	
Axillary surgery			NS
Axillary dissection	28 (72%)	28 (62%)	
Sentinel lymph node dissection	20 (51%)	21 (47%)	
Sentinel lymph node dissection then axillary dissection	10 (26%)	6 (13%)	
No axillary surgery	1 (3%)	2 (4%)	
RT characteristics			
Breast RT	35 (90%)	38 (84%)	NS
Median dose (Gy)	50 (40–50)	50 (40–50)	NS
Dose per fraction			
≤2 Gy	27 (77%)	27 (71%)	NS
2–5 Gy	8 (23%)	10 (26%)	
Missing data	0 (0%)	1 (3%)	
Irradiation technique			
Dorsal decubitus	30 (86%)	31 (82%)	NS
Lateral decubitus	5 (14%)	6 (16%)	
Missing data	0	1 (3%)	
Boost	35 (90%)	38 (84%)	NS
Median dose (Gy)	16 (10–18)	16 (10–26)	NS
Type of radiation			
Photons	20 (57%)	13 (34%)	NS
Electrons	10 (29%)	15 (39%)	
Photons and electrons	5 (14%)	10 (26%)	
Chest wall RT	4 (10%)	7 (16%)	NS
Median dose (Gy)	50 (40–50)	50 (40–50)	NS

(Continued)

Table 2. (Continued)

Radiotherapy characteristics	Bevacizumab + RT, <i>n</i> (%)	RT alone, <i>n</i> (%)	<i>p</i> -value
Dose per fraction			
≤2 Gy	3 (75%)	6 (86%)	NS
>2 Gy	1 (25%)	1 (14%)	
Type of radiation			
Photons	2 (50%)	2 (29%)	
Electrons	1 (25%)	3 (43%)	NS
Photons and electrons	1 (25%)	1 (14%)	
Lymph node RT	19 (49%)	21 (47%)	NS
Supraclavicular nodes	17 (44%)	20 (44%)	NS
Internal mammary nodes	12 (31%)	14 (31%)	NS
Axillary nodes	1 (3%)	1 (2%)	NS
RT duration (days)			NS
Breast RT and boost ± lymph node irradiation	49 (29–63)	49 (28–80)	
Missing data	2 (6%)	4 (10%)	
Chest wall RT ± lymph node irradiation	38 (35–43)	38 (28–42)	
Missing data	1 (25%)	0	
Median interval between surgery and RT (days)	184 (125–303)	186 (110–239)	NS

NS, not significant; RT, radiotherapy.

13 patients, grade 1 for 9 patients, grade 2 for 3 patients and no grade 3 results were observed. Cosmetic assessment was performed for 26 (58%) patients in the arm without concurrent bevacizumab. Cosmetic results were grade 0 for 16 patients, grade 1 for 10 patients, and no grade 2 or 3 results were observed (Table 3).

Late toxicities 1 year after the completion of radiotherapy

Late toxicities at 1 year after the completion of RT were available for 38 (97%) patients in the bevacizumab arm and 40 (89%) patients in the arm without bevacizumab, respectively.

Grade 1–2 toxicities reported in the bevacizumab arm were pain in seven (18%) patients, fibrosis in three (8%) patients, telangiectasia in two (5%) patients and dyspnoea in one (3%) patient. No grade 3–4 toxicities were observed.

Grades 1–2 toxicities reported in the arm without concurrent bevacizumab were pain in six (15%) patients, fibrosis in two (5%) patients, lymphoedema in two (5%) patients and paresis in two (5%) patients. No grade 3–4 toxicities were observed.

No significant difference was observed between the two arms in terms of grade 1–2 toxicities or grade 3–4 toxicities (Table 5).

Cardiovascular toxicity 1 year after the completion of radiotherapy

In the database, among patients in the arm with B-RT, one bradycardia episode occurred in one patient after the completion of RT. In the arm without bevacizumab, a deep venous thrombosis

occurred in one patient after the end of RT. With regard to left ventricular ejection fraction (LVEF), evaluation 1 year after the completion of RT was available for 41 (91%) patients treated by RT alone and for 36 (92%) patients treated with the concurrent association of B-RT. Only one patient in the arm with B-RT experienced a LVEF value <50% 1 year after the end of RT (44%) (Table 4). She was 49 years old, presented no cardiovascular risk factors and received RT to the left breast plus a boost to the tumour bed.

DISCUSSION

In this work studying the population of the BEATRICE randomized trial, we compared the acute and late toxicity rates between the experimental arm comprising concurrent bevacizumab (39 patients) and the standard arm without bevacizumab (45 patients). A low rate of toxicity was observed in both arms and no significant difference was observed between the two arms in terms of acute toxicities, cosmetic results and late toxicities. These results concerning acute toxicity are therefore comparable to those reported by Goyal *et al*,² while also providing an analysis of oesophageal toxicity, cosmetic effects and late toxicity.

Phase 2 or 3 studies have been conducted in the adjuvant setting in order to achieve an improvement of disease-free survival for patients with Stages II and III BC with or without human epidermal growth factor receptor 2 overexpression by using various combinations of chemotherapy and various durations of treatment.^{1,4} Despite the acceptable acute and late 1-year locoregional toxicity of concurrent RT and bevacizumab

Table 3. Acute toxicities and cosmetic results

Evaluation of toxicity	Bevacizumab + RT, <i>n</i> (%)	RT alone	<i>p</i> -value
Acute dermatitis			
Acute dermatitis evaluation			NS
Yes	35 (90%)	41 (91%)	
No	4 (10%)	4 (9%)	
Grade			NS
Grade 0	5 (14%)	7 (17%)	
Grade 1	18 (51%)	24 (59%)	
Grade 2	9 (26%)	8 (20%)	
Grade 3	3 (9%)	2 (5%)	
Grade 4	0	0	
Acute oesophagitis evaluation			NS
Yes	39 (100%)	44 (98%)	
No	0 (0%)	1 (2%)	
Grade			NS
Grade 0	38 (97%)	44 (100%)	
Grade 1	0	0	
Grade 2	1 (3%)	0	
Grade 3	0	0	
Grade 4	0	0	
Cosmetic results			
Cosmetic evaluation			NS
Yes	25 (64%)	26 (58%)	
No	14 (36%)	19 (42%)	
Cosmetic results			NS
Grade 0 (no change)	13 (33%)	16 (36%)	
Grade 1 (minor changes)	9 (23%)	10 (22%)	
Grade 2 (operated breast deformed)	3 (8%)	0	
Grade 3 (operated breast seriously deformed)	0	0	

NS, not significant; RT, radiotherapy.

observed in this study, the addition of bevacizumab in the adjuvant setting did not improve progression-free survival, and bevacizumab is therefore not indicated in this setting.¹

As bevacizumab increased progression-free survival in metastatic BC and pCR after neoadjuvant therapy, a potential application suggested by this study would be concurrent bevacizumab and locoregional RT for the treatment in this indication or of metastatic BC. In order to improve the locoregional control of patients with metastatic BC, it is now generally accepted that, in addition to systemic therapy, treatment of the initial breast disease by RT alone, surgery alone or a sequential combination of surgery and RT must be considered. Several studies have also suggested that treatment of the initial breast tumour is associated with improved

survival in patients with BC with synchronous metastases.⁵ In a retrospective study, Le Scodan et al⁵ showed that locoregional treatment by RT alone allowed improvement of the 3-year overall survival for patients with BC and visceral metastases (34.2% vs 17.8%; $p = 0.005$). After treatment of patients with metastatic BC by bevacizumab in combination with taxane-based chemotherapy, continuation of bevacizumab concurrently with locoregional breast RT for 6.5–8 weeks may be able to maintain control of metastatic disease while preserving the patient's quality of life. In particular, concurrent B-RT could be useful in triple-negative metastatic BC for which no chemotherapy is administered during RT. However, continuation of concurrent B-RT cannot be recommended for metastatic BC in the absence of data beyond 1 year.

Table 4. Left ventricular ejection fraction (LVEF) evaluation 1 year after radiotherapy (RT)

Cardiac toxicity	Bevacizumab + RT, <i>n</i> (%)	RT alone, <i>n</i> (%)	<i>p</i> -value
LVEF evaluation before any treatment			
Yes	37 (95%)	45 (100%)	
No	2 (5%)	0	
LVEF			NS
<50%	0	0	
>50%	37 (95%)	45 (100%)	
Missing data	2 (5%)	0	
LVEF evaluation 1 year after the RT			
Yes	36 (92%)	41 (91%)	
No	3 (8%)	4 (10%)	
LVEF			NS
<50%	1 (3%)	0	
>50%	34 (87%)	41 (91%)	
Missing data	4 (10%)	4 (10%)	

NS, not significant.

The results of this multicentre study with 1-year follow-up indicate the acceptable toxicity of concurrent bevacizumab and locoregional RT for BC. Nevertheless these results need to be confirmed with longer follow-up.

Table 5. Late toxicities

Late toxicities	Bevacizumab + RT, <i>n</i> (%)		RT alone, <i>n</i> (%)	
Late toxicities evaluation				
Yes	38 (97%)		40 (89%)	
No	1 (3%)		5 (11%)	
	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4
Pain	7 (18%)	0	6 (15%)	0
Fibrosis	3 (8%)	0	2 (5%)	0
Telangiectasia	2 (5%)	0	0	0
Arm lymphoedema	3 (8%)	0	2 (5%)	0
Ulceration	0	0	0	0
Myocardial ischaemia	0	0	0	0
Pericarditis	0	0	0	0
Dyspnoea	1 (3%)	0	0	0
Dysphagia	0	0	0	0
Paresis	0	0	2 (5%)	0

RT, radiotherapy.

FUNDING

Data collection was supported by Roche France.

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