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Original article

Primary systemic treatment and concomitant low dose radiotherapy for breast cancer: Final results of a prospective phase II study

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ABSTRACT

Background: To evaluate the efficacy of preoperative low dose fractionated radiotherapy (LD-FRT) and chemotherapy in breast cancer.
Materials and methods: Patients with stage IIA–IIIA breast cancer, received LD-FRT (0.40 Gy bid, on day 1 and 2, for 6 cycles) to primary tumor volume and concurrent chemotherapy with non-pegylated liposomal anthracycline and docetaxel. Pathological response was assessed by Mandard Tumor Regression Grade (TRG). We evaluated the pathological major response rate (PMRR) as TRG1 and TRG2. The expected outcome was a PMRR of 60%. The accrual was determined by the single proportion powered analysis ($\alpha = 0.05$, power $= 0.8$).
Results: Twentyone patients were enrolled. No grade 2–4 acute skin and hematological toxicity was observed. TRG1 was obtained in 3 patients (14.3%), TRG2 in 4 patients (19%). The PMRR was 33.3%; it does not concur with the expected result, but is similar to that of chemotherapy alone. According to molecular subtype, 2/11 *luminal A* patients and 4/6 *luminal B* patients obtained a PMRR to preoperative treatment (35.3%); 1/4 *basal like* patients reported TRG1 (25%).
Conclusions: LD-FRT concomitant with primary systemic treatment has a good toxicity profile. The response rate is consistent with that of chemotherapy alone, and suggests different interactions between low dose radiotherapy and molecular subtypes. Additional investigations are planned.

Introduction

Primary systemic treatment in breast cancer has historically had the aim of reducing unresectable tumors, allowing surgery. For operable tumors, primary chemotherapy could allow a greater rate of breast conservative surgery, reducing the use of mastectomy [1,2]. Moreover the clinical implementation of primary chemotherapy appears to improve disease free survival (DFS) and overall survival (OS) rates in breast cancer [3,4]. Primary endpoint of preoperative chemotherapy is the histological tumor response, because it positively correlates with long-term patient survival, and several studies aim to increase the rate of pathological complete response through the association of various chemotherapeutic agents [3–8]. Over the last 30 years, a broad spectrum of different chemotherapeutic agents has been tested in the preoperative setting. Based upon these results, the respective consensus statements of the 2009 and 2011 St. Gallen Conferences stated that primary systemic treatment regimens should contain an anthracycline and a taxane [9,10]. Anthracycline and taxane-based therapies are widely used in combination or sequential regimens, with pathological tumor response rates ranging between 22% and 31% [11,12]. While conventional doxorubicin has demonstrated excellent antitumor activity in patients with breast cancer, its clinical utility is limited due to its acute toxicities and the potential for causing cumulative cardiac damage [13]. An attempt to improve the therapeutic index of anthracyclines, reducing their toxicities, is drug encapsulation in liposomes. We know that liposomal doxorubicin and pegylated liposomal doxorubicin are active in

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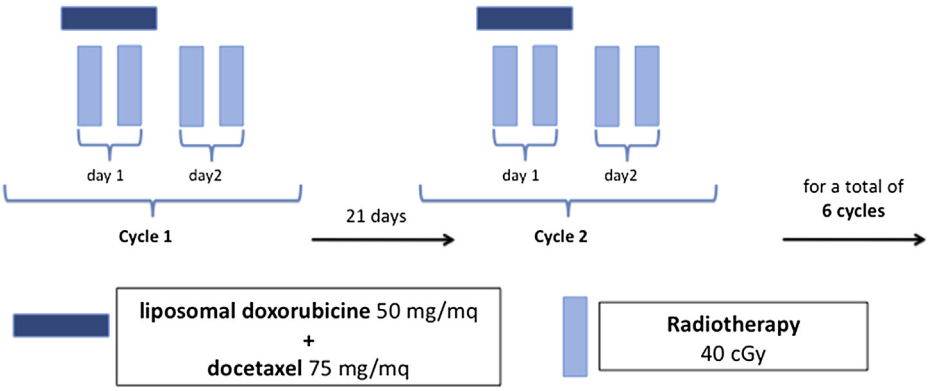

Fig. 1. Treatment schedule.

metastatic breast cancer, but several early clinical trials have shown their efficacy and tolerability as primary therapy for locally advanced breast cancer, showing promising results in terms of response rate, which motivate further studies of combined preoperative regimens that incorporate pegylated liposomal doxorubicin [14].

Preoperative chemotherapy and concomitant radiotherapy have been proposed for different kind of tumors [15,16]. Several studies reported encouraging results about preoperative chemoradiation with taxanes and other chemotherapy regimens for locally advanced breast cancer patients [17–20]. Several cancer cell lines have shown low-dose hyper-radiosensitivity (HRS) at doses <1 Gy; in particular, radiation doses below 0.5 Gy seem to be more effective per unit dose than higher doses. Conversely, an increased radioresistance (IRR) per unit dose to cell killing by radiation has been reported at doses between 0.5 and 1 Gy [21–23]. *In vitro* data showed that LD-FRT acts as a chemo-potentiator, without increasing toxicity [24]. Preliminary results of clinical trials on the association of LD-FRT with chemotherapy suggest the feasibility and effectiveness of this new approach [25–28].

In our Institution, we conducted a phase I study, in order to evaluate the feasibility of preoperative LD-FRT in breast cancer, in association with two anthracycline–docetaxel regimens, demonstrating that this new treatment paradigm is feasible and well tolerated, with a toxicity profile similar to that of chemotherapy alone. We obtained a good histological response, with a Tumor Regression Grade (TRG) 1-2 rate of 80% [29]. On this setting, we started a single arm phase II study in order to evaluate the efficacy of LD-FRT and concomitant primary systemic treatment with liposomal anthracycline and docetaxel in terms of pathological response rate and TRG in stage IIA-B and IIIA breast cancer.

Materials and methods

Eligibility criteria were: histological breast cancer diagnosis obtained by core-needle biopsy, no previous treatment, age ≥18, ECOG score 0–2, no evidence of distant metastases, normal hematopoietic, liver, renal and cardiac functions. Patients with c-ErbB2 expression grade 3+, presence of extensive intraductal component, pregnant or in the breastfeeding phase at the time of diagnosis, or with previous or current diagnosis of malignancies other than breast cancer were ineligible.

The study was approved by our institutional review board and by ethics committee. All patients provided a written and informed consent before receiving treatment.

All patients were clinically evaluated by a surgeon and a radiation oncologist. Baseline assessment included a complete clinical examination, mammography, breast ultrasound, breast contrast-enhanced magnetic resonance imaging (MRI), complete cell blood count and serum chemistry, chest and abdomen computed tomography, bone scan, electrocardiogram and cardiac sonography. MRI was performed at baseline, after three cycles of treatment, and before surgery, since patients were part of a diagnostic protocol active in our Institution [30]. After clinical and radiologic examination, a multidisciplinary team assigned the clinical stage. Tumors were classified according to the International Union Against Cancer TNM 7th edition. Histological grading, hormone receptor status, HER-2-neu expression and Ki-67 rate were evaluated before treatment.

Treatment plan is summarized in Fig. 1. Patients were assigned to receive 6 cycles of liposomal anthracycline (50 mg/mq) and docetaxel (75 mg/mq) on day 1 of a 21-day cycle, concurrent with LD-FRT (2 fractions of 0.4 cGy b.i.d on days 1 and 2; total dose 1.6 Gy for 1 cycle). The first RT fraction was delivered before chemotherapy administration, the second fraction was given at least 5–6 h later. The cycle was repeated every 21 days, for a total planned dose of 9.6 Gy (6 cycles, for a total treatment time of 126 days).

A CT-based planning was used. Patients were scanned in a standard supine position, using a breast board. A radiation oncologist defined the gross tumor volume (GTV), which included the target lesion identified by clinical examination and in pretreatment imaging studies. The clinical target volume (CTV) was obtained adding 10 mm to the GTV, to take into account the suspected subclinical malignant disease; the planning target volume (PTV) was defined as the CTV + 5 mm of margin, to consider internal and set-up errors [31]. Axillary lymph nodes were not included in the treatment volume, even if clinical or radiological involved.

After 3 weeks from the end of primary systemic treatment, patients underwent clinical and radiological re-examination with mammography, ultrasound and MRI. No clinical and radiological evidence of tumor in the breast and axillary lymph nodes was defined as a clinical Complete Response (cCR). Reduction in total tumor size of 50% or greater was graded as a clinical partial response. Six to eight months after the end of primary chemoradiation treatment, patients underwent breast surgery and axillary node dissection. If breast conservative surgery was not possible, patients were submitted to modified radical mastectomy. Immuno-histochemical evaluation of estrogen and progesterone receptors (ERs, PRs), HER-2-neu and Ki-67 was performed on surgical specimen. We used the molecular subtypes definition recommended by St. Gallen 2013 Consensus [32]. Four to six weeks from surgery patients started conventional 3D tangential radiotherapy ± adjuvant chemotherapy ± hormonal therapy,

according to prognostic markers and risk factors. Radiation therapy was delivered to the whole breast or to the chest wall, for a total dose of 50.4 Gy. Patients with 4 or more positive axillary nodes received radiotherapy to infraclavicular region and supraclavicular area [33,34]. Patients with residual nodes disease (4 or more positive lymph nodes) were submitted to adjuvant chemotherapy.

Primary endpoint of the study was the evaluation of the response rate. Tumor response was defined according to Mandard TRG score [35]. TRG1 defines the complete response with the absence of residual cancer and fibrosis extending through the tumor margin; TRG2 describes the presence of residual isolated cells scattered through the fibrosis; TRG3 is the increase in number of residual cancer cells, with fibrosis predominating; TRG4 defines the residual cancer outgrowing the fibrosis; TRG5 describes the absence of regressive changes. TRG1 and TRG2 represent the pathological major response. Tumor response was investigated by a pathologist, and analyzed by an independent and blinded committee of expert pathologists.

Secondary endpoint was the assessment of toxicity. Toxicity was evaluated according to EORTC/RTOG toxicity scale [36]. Skin toxicity was recorded after each cycle of LD-FRT and chemotherapy, hematological toxicity was evaluated every week. Preventive granulocyte colony-stimulating factors were administered after each chemotherapy cycle, in order to keep the rate of adverse effects caused by neutropenia and infection low [37,38].

The analysis of response proportion was performed by single proportion test and the validation of the accrual was determined by the single proportion powered analysis (Systat 11, SPSS Science, Chicago, IL, USA). We assumed H0 ("bad" response probability) equal to 30%, according to literature and H1 ("good" response probability) equals to 60%, according to a previous study [4,13,14,18,39–45]. The number required to detect a difference of 60% versus 30% ($\alpha = 0.05$, power $= 0.8$) was 21.

Results

Between March 2009 and September 2011, 21 patients with stage IIA-B and IIIA breast cancer were enrolled. The median age was 51 years (range, 32–75). The clinical stage was IIA (*c*T2N0M0) in 6 patients (28.6%), IIB (*c*T2N1M0) in 13 patients (61.9%) and IIIA (*c*T3N1M0- *c*T3N2M0) in 2 patients (9.5%). The cell type was invasive ductal carcinoma in 18 patients (85.7%) and invasive lobular carcinoma in 3 patients (14.3%). The molecular subtype was *luminal A* in 11 patients (52.4%), *luminal B* in 6 patients (28.6%), *basal like* in 4 patients (19%). Median tumor size, measured as the largest orthogonal diameter on MRI, was 4 cm (range, 1.6–6.7) before preoperative treatment, and 1.7 cm (range, 0–5.0) at the end (Table 1).

All patients completed the planned treatment: for each patients 6 cycles were administered, for a total dose of LD-FRT of 9.6 Gy. Patient compliance to treatment was good. The pathological response was classified as TRG1 in 3 patients (14.3%), TRG2 in 4 patients (19%), TRG3-5 in 14 patients (66.6%). The pathological major response rate (PMRR: TRG1 and TRG2) obtained was 33.3%. These results were analyzed by an independent and blinded committed, who found four minor conflicts for TRG 3-5 patients; no conflicts were found for other patients, especially for TRG 1-2 patients. A detailed description of tumor response according to clinical and pathological stage is reported in Table 2.

There were no grade 2–4 hematological events. Grade 1 hematologic toxicity was observed in 6 patients (anemia and leuconeutropenia). There were no severe infections due to neutropenia. Most common non-hematological toxicities reported were nausea, diarrhea and alopecia, which occurred in all patients.

Table 1
Patients characteristics.

	$N = 21$
Age, years	
Range	32–75
Mean	51
Menopausal status	
Premenopausal	10
Postmenopausal	11
Clinical stage	
IIA	6
IIB	13
IIIA	2
Tumor size	
2–5 cm	19
>5 cm	2
Histology	
Invasive ductal cancer	18
Invasive lobular cancer	3
Histologic grade	
G1	1
G2	12
G3	8
Molecular subtypes	
Luminal A	11
Luminal B	6
Triple negative	4

Grade 1 acute skin toxicity was observed in 1 patient. No acute skin toxicity $\geq$ grade 2 was reported. There were no cardiac events.

All patients underwent surgery: 18 patients (85.7%) had quadrantectomy, 3 (14.3%) patients were submitted to mastectomy with breast reconstruction. We did not observe any postoperative complications. Adjuvant radiotherapy was delivered to the whole breast in 18 patients; infra and supraclavicular irradiation was administered to 6 patients with $\geq$4 positive lymph nodes. After surgery and radiotherapy, 4 patients with residual nodal disease were assigned to receive adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil for 6 cycles. Five patients with hormonal receptors positive, received tamoxifen and LH–RH analogue, 3 patients received only tamoxifen and 8 patients aromatase inhibitors.

Median follow-up was 31 months. At the time of analysis all patients were alive, 2 patients had distant metastasis at 4,8 and 1,3 months from diagnosis, respectively.

Discussion

Primary systemic treatment is the standard for management of stage IIA-IIB/IIIA breast cancer. Primary aim is the achievement of a pCR, which is correlated to a better 10-year OS and DFS and a lower risk of recurrences [3–5]. A wide variety of chemotherapy regimens have been used as preoperative treatment, with most incorporating doxorubicin. These regimens generally determine a response rate in at least two-thirds of patients with a complete pathological remission rate of roughly 10–15% [4]. Anthracyclines, such as doxorubicin, are considered among the most active single agents in advanced breast cancer. However, the use of anthracyclines is limited by their acute toxicities and by their cumulative cardiac damage. An attempt to improve the therapeutic index of anthracyclines includes drug encapsulation in liposomes. The encapsulation of a cytostatic agent within a vector such as a liposome, significantly reduces its diffusion and consequently the toxicity for healthy tissue, while increasing the concentration within the tumor. Several clinical trials evaluated the effectiveness of non-pegylated and pegylated liposomal anthracyclines and have shown them to have similar efficacy with less cardiac toxicity when

Table 2
Tumor response according to clinical and pathological stage.

Patients	Clinical Staging cTNM	Tumor size (cm) in RM prior LDFRT and CT	Tumor size (cm) in RM post LDFRT and CT	Ki 67 rate prior LDFRT and CT (%)	Pathological staging ypTNM	Ki 67 rate post LDFRT and CT (%)	Molecular subtype	TRG	TRG revision by external committee
1	T3N1M0	5.5	1.5	25	T1mN1a	7	Luminal B	TRG3	TRG3
2	T2N0M0	4.2	0	3	T1micN1micM0	70	Luminal A	TRG1	TRG1
3	T2N1M0	4.0	0	80	T0N0M0	–	Triple neg	TRG1	TRG1
4	T2N1M0	2.5	2.5	30	T1micN2aM0	1	Luminal B	TRG2	TRG2
5	T3N1M0	6.7	5.0	45	T2N3aM0	20	Luminal B	TRG4	TRG4
6	T2N0M0	2.9	2.9	90	T1aN0M0	90	Triple neg	TRG4	TRG5
7	T2mN1M0	3.5	2.2	1	T1micN1aM0	1	Luminal A	TRG2	TRG2
8	T2N1M0	3.2	1.0	40	T1bN2aM0	25	Luminal B	TRG3	TRG4
9	T2N1M0	4.4	4.4	15	T2N1aM0	12	Luminal A	TRG4	TRG4
10	T2N1M0	3.4	3.4	25	T2N1aM0	20	Luminal B	TRG5	TRG5
11	T2N0M0	3.0	0.4	80	T1aN0M0	3	Luminal B	TRG2	TRG2
12	T2N1M0	3.0	0	35	T0N0M0	–	Luminal B	TRG2	TRG2
13	T2N1M0	5.0	5.0	20	T2N0M0	20	Luminal B	TRG5	TRG5
14	T2N1M0	3.0	1.7	45	T2N3aM0	70	Luminal B	TRG4	TRG4
15	T2N1M0	3.0	1.5	12	T2N2aM0	5	Luminal A	TRG3	TRG3
16	T2N0M0	3.2	1.5	3	T1cN0M0	3	Luminal A	TRG3	TRG4
17	T2N1M0	3.5	2.7	70	T2N0M0	90	Triple neg	TRG4	TRG5
18	T2N1M0	2.2	3.1	70	T2N0M0	90	Triple Neg	TRG4	TRG4
19	T2N0M0	2.7	1.6	12	T1cN0M0	4	Luminal A	TRG3	TRG3
20	T2N0M0	2.3	1.7	25	T1cN0M0	8	Luminal B	TRG3	TRG3
21	T2N0M0	4	0	70	T0N0M0	–	Luminal B	TRG1	TRG1

compared with free doxorubicin [46–48]. Radiotherapy involving the heart region is one of the possible risk factors for anthracycline cardiotoxicity, so in an effort to prevent or reduce this effect liposomal anthracyclines has been administered in our trial. Taxanes are strongly active in breast cancer treatment. Concomitant use of docetaxel and anthracyclines led to a clinical overall response rates of 77–96%, and to a breast conservation rate of 89% [7,49,50]. There are only few experience about the concomitant administration of taxanes and radiotherapy in breast cancer, proving the safety and the efficacy of this association [51].

The role of preoperative radiotherapy in breast cancer treatment, sequential or concomitant to chemotherapy, has been explored in some studies. Formenti and colleagues examined the role of primary concurrent paclitaxel and radiotherapy for patients with locally advanced breast cancer; they obtained a pCR in 16% of patients, with a marked grade 3 skin toxicity and a high rate of surgical complications (14%) [19]. In a subsequent study they reported that pathologic response to concurrent paclitaxel-radiation translated into superior DFS and OS, and that half of the patients with hormonal receptor negative tumors achieved a pathologic response [17–20]. Administration of LD-FRT to the primary tumor, instead of standard fractionation to the whole breast, concomitant with chemotherapy in preoperative setting could reduce acute skin toxicity and post-surgical complications.

Several preclinical and clinical studies have proved the HRS phenomenon at low dose of radiotherapy and the chemosensitizing effect of LD-FRT [21–29]. Mammalian cells exhibit HRS to radiation doses less than 0.3–0.6 Gy [21,22,52]. HRS does not activate cellular repair mechanisms, often observed at clinically relevant or higher radiation doses, and thus could explain why there is no induction of radiation resistance with HRS as measured *in vitro* [21]. Furthermore, HRS failed to induce prosurvival transcription factors, that are necessary for increasing the levels of MDR-1 gene [53]. Hence, no MDR-1 induction in response to LD-FRT will help to increase the effects of chemotherapy, that is often mitigated by MDR-1 [54]. The use of LD-FRT with chemotherapy provides a new strategy to improve tumor downstaging through the use of radiotherapy as a biological modifier of the chemotherapy response. Combined chemo-radiotherapy strategies to enrich the G2-phase fraction before radiotherapy obtained promising results in experimental setting. LD-FRT has been combined with cell synchronization using taxanes to radiosensitize squamous cell carcinoma of head and neck in nude mice tumor xenografts: low doses of radiation (0.1–0.6 Gy) were found to induce HRS phenomenon, and doses more than 1Gy demonstrated IRR [55,56]. These data supported the use of LD-FRT as a chemopotentiator in several investigative clinical trials. A phase I trial reported that LD-FRT to the upper abdomen was well tolerated at 0.6 Gy per fraction when combined with gemcitabine in patients with pancreatic cancer [57]. In patients with locally advanced head and neck cancer LD-FRT were used as induction therapy in a pilot trial, in combination with carboplatin and taxol, with good results in terms of response rate and toxicity profile. [25] In our Institution several experiences has been conducted with LD-FRT and concomitant chemotherapy. Concurrent palliative chemotherapy and LD-FRT have been evaluated in patients with various type of epithelial tumors; the overall response rate was 45% with low toxicity [26]. A prospective phase II study demonstrated that LD-FRT combined with pemetrexed in patients affected by recurrent non small cell lung cancer is a feasible and well tolerated novel approach, with a response rate of 42% [27]. A phase I study reported that concomitant LD-FRT and chemotherapy with non-pegylated liposomal anthracycline and docetaxel is a feasible preoperative approach in treatment of IIA-B/IIIA stage breast cancer. The skin and hematological toxicity profile was very low, and we not observed cardiac toxicity or postsurgical complications; the PMRR obtained was 80% [29]. Considering these results we started a single arm phase II study in order to evaluate the efficacy of this new primary treatment approach.

The expected pathological major response rate of 60% was not achieved, but the obtained result of 33.3% was consistent with that of chemotherapy alone (pCR, 23–29%) [39,40]. Several early clinical trials have shown the efficacy and tolerability of liposomal doxorubicin and pegylated liposomal doxorubicin as primary systemic treatment in association with paclitaxel or docetaxel for locally advanced breast cancer [41–45]. They all obtained good results in terms of response rate, with a pCR rate of 7–16%, that is similar to that reported by our trial. It should be noted that in our trial we considered both TRG1 and TRG2 as a pathological major response (33.3%), on the basis of clinical and histopathological findings: our

pathologist and the independent committee agreed about the observation that LD-FRT induces a greater fibrotic reaction than chemotherapy alone, which encases the residual tumor. This finding is supported by the evidence that LD-FRT could have an effect also on the inflammatory cellular components of tumors, by decreasing the number of cells, reducing the tumor-associated interstitial edema, and modifying the biochemical microenvironment, which support the tumor growth [58].

A recent metanalysis provides evidence of an independent association between breast cancer molecular subtype and pCR, observing that *basal like* patients are more responsive to chemotherapy (pCR 31.1%) than *luminal A-B* patients (pCR 8.3%) [59]. In our study *luminal A-B* patients obtained a pathological major response rate higher then *basal like* subtype (35.3% versus 25%), suggesting a possible mechanism of interaction of LD-FRT with different molecular subtypes. However the low statistical power, due to the small sample size of the study, cannot reliably rule out the importance of these biomarkers in terms of pathological response.

No evidence was found that LD-FRT increases the rate of radiation-induced toxicity; we did not observe cardiotoxicity, pneumonitis and serious skin reactions. For local failure rates, late toxicity and cosmetic outcome longer follow-up is needed.

Our results demonstrated that the combination of LD-FRT and chemotherapy with liposomal anthracycline and docetaxel is well tolerated, with a toxicity profile similar to chemotherapy alone. Nevertheless the expected increase of response has not been observed, so further research steps are directed towards increasing the number of patients with different molecular subtypes, in order to provide results that may change practice in chemoresistant breast cancer subtypes.

Conclusions

Results of this phase II study demonstrated that preoperative low dose radiotherapy and concomitant chemotherapy with non-pegylated liposomal doxorubicin and docetaxel have a low toxicity profile. The pathological major response rate obtained on primary tumor is similar to that of chemotherapy alone, and suggests different interactions of low dose radiotherapy with various breast cancer molecular subtypes. Additional investigations are warranted.

Conflict of interest statement

All authors declare no conflict of interest.

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Ethical approval

The study was approved by ethics committee.

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