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Advanced chemoresistant luminal B breast cancer patients' treatment improvement by a combination of liposomal pegylated doxorubicin and local Magnetothermy (regional inductive mild hyperthermia) compared to dose-dense therapy and local Magnetothermy (regional inductive mild hyperthermia)

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Abstract

Although a growing variety of more targeted therapeutic approaches for various breast tumor subtypes are now available, traditional chemotherapy remains the primary treatment choice. Long-term survivors of advanced breast cancer are uncommon, with 5-year survival rates ranging between 13% and 35%. It is somewhat strange, but in principle evident, that the proportion of relapses is also larger with advanced resistant BC forms: a recurrence occurs after 1 year – 14,6%; 2 years - 33.8%; and 5 years (peak) up to 83%. According to the American Cancer Society, more than 30% of breast cancers exhibit initial resistance to chemotherapy. The targeted transport of anticancer drugs using a carrier system (microencapsulation drugs) against the background of Magnetothermy contributes to increased drug penetration into the tumor cell. The best combination regimen based on liposomal pegylated doxorubicin (LPD) is currently being developed. The aim to get and enhance the therapeutic benefits resulted from the synergetic effect from the combination of liposomal pegylated doxorubicin (LPD) and Magnetothermy (regional inductive mild hyperthermia) modification against advanced chemoresistant luminal B breast cancer to overcome several challenges, including side effects of anthracyclines, lower clinical tumor answer, limited stability. Based on the safety and efficacy data for Liposomal Pegylated Doxorubicin (LPD), a study was proposed in which 60 patients advanced Luminal B1 breast cancer stabilization (by RECIST 1.1), e.g, chemoresistant; were randomized to receive one of the following two alternatives: first – intravenous infusion during sixty minutes liposomal pegylated doxorubicin (LPD) 50 mg/m^2 and thirty minutes after drug infusion Local Magnetothermy during 30 minutes every four weeks – 4 cycles (30 patients); second group – AC (Doxorubicin 60 mg/m2 and Endoxan 600 mg/m2 and thirty minutes after drug infusion Local Magnetothermy during 30 minutes every two weeks (Dose-Dense therapy (DDT)) – 4 cycles every 14 day (30 patients). The overall efficacy of treatment for patients with resistant lum B1 BC assigned to the first group was 73.33%, while in the second 60.00%. Combined MT RIMH and liposomal pegylated chemotherapy increased the overall efficacy of treatment by 13.33% ($\chi 2$=9.076; P<0.02). Liposomal anthracyclines have been demonstrated to be effective and safe in advanced chemoresistant Lum B breast cancer when combined with Magnetothermy (regional inductive mild hyperthermia). Adding Magnetothermy (regional inductive mild hyperthermia) to chemotherapy significantly improved response rate, progression-free survival, and overall survival. In the neoadjuvant therapy of breast cancer, the LPD-containing regimen+MT and DDT+MT regimens had comparable efficacy but differ in toxicity.

Keywords: liposomal pegylated doxorubicin; advanced chemoresistant luminal B1 breast cancer; dose-dense therapy; magnetothermy (regional inductive mild hyperthermia); combined treatment planning.

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1. Introduction

Breast cancer (BC) alone accounts for 30% of all new cancer diagnoses in women and around 15% of all deaths in Ukraine [1]. In recent years, there has been a considerable advancement in our understanding of cancer and how it has been translated into advancements in complete therapy [2]. Although a growing variety of more targeted therapeutic approaches for various breast tumor subtypes are now available, traditional chemotherapy remains the primary treatment choice [3]. Despite the fact that luminal B tumors are highly proliferative, they are less likely to react to neo-adjuvant chemotherapy, hence resistance is common. Luminal B1 (er+; pr-; Her2-; Ki67>30%) is one of the breast cancer subtypes that requires novel markers to customize preoperative chemotherapy prescription and identify those patients who would gain the most from treatment while experiencing the least amount of chemotherapy harm. [4]. Long-term survivors of advanced breast cancer are uncommon, with 5-year survival rates ranging between 13% and 35%. It is somewhat strange, but in principle evident, that the proportion of relapses is also larger with advanced resistant BC forms: a recurrence occurs after 1 year – 14,6%; 2 years - 33.8%; and 5 years (peak) up to 83%. [5]. After thorough therapy, advanced luminal B BC had a considerably greater risk of local recurrence and distant metastases than advanced luminal A (11.43% vs 4.38%, respectively) - first year; 31.35% of relapses occurred within 2 years of surgery (35.62% luminal A group, 30.15% luminal B1 group), 82.81% - both patients relapsed [6]. Improve chemotherapy treatments have focused on use drugs and different modifications, that have a direct influence on specific breast cancer types, therefore prolonging medication action and targeting malignant cells to minimize toxic side effects [7]. According to the American Cancer Society, more than 30% of breast cancers exhibit initial resistance to chemotherapy [8], anthracycline antibiotic resistance affects thirty percent of these people, ranging from 42% to 51%. One method to enhancing treatment results is to overcome drug resistance by modifying the features of scheme treatment and the microenvironment of the tumor [9]. The targeted transport of anticancer drugs using a carrier system (microencapsulation drugs) against the background of Magnetothermy contributes to increased drug penetration into the tumor cell due to improved redox processes, increased drug effectiveness inside the tumor cell, significantly reduced exposure of normal tissues, and changing the tumor microenvironment (reduction of inflammation manifestations) [10]. Liposomal forms are made of phospholipids with a hydrophilic "head" and a hydrophobic "tail," which ensures their transport function (delivery of drugs in liposome composition to cells, their size ranges from 20 to 200 nanometers and is determined by the maximum amount of drug stored within the membrane and its flexibility) and passage through the cell membrane via endocytosis [11]. Liposomes developed as drug delivery devices to alter medication pharmacokinetics and distribution in order to reduce the toxicity of chemotherapy [12]. The amount of chemotherapeutic medication delivered to the tumor is determined by coating these delivery systems with polymers, namely polyethylene glycol (PEG), which helps liposomes to evade the immune system and so enhance circulation time in the circulatory system [13]. Pegylated liposomes have a longer half-life than nonpegylated liposomes when generated in this manner, according to studies (varying from a few hours to 45 hours) [14].

Magnetothermy is a promising treatment option for advanced breast cancer [15], based on the impact of an electromagnetic field on a tumor region, during which time-varying magnetic fields create eddy currents, inducing heating (<40°C) and changes in the tumor's redox state [16]. Electromagnetic radiation may control the anticancer impact of medications via the free radical mechanism, the action of these agents in the tumor region is likewise influenced by magnetothermy [17]. Absorption of electromagnetic radiation can bring a personalized approach to neoadjuvant therapy by boosting the efficacy of chemotherapy and further protecting the breast after surgery, hence raising the proportion of organ-preserving and oncoplastic surgeries [18].Combined with chemotherapy, magnetothermy dramatically improves the rate of response and overall survival, prolong time to progression, when compared to chemotherapy alone [19]. A dose-dense regimen is the best neoadjuvant chemotherapy for individuals with high-risk early recurrence breast cancer [20], a dose-dense chemotherapy schedule did improve PFS. The study aimed to compare dose-dense chemotherapy (given every two weeks) with standard-interval chemotherapy (given every three weeks), as well as the combination epirubicin, cyclophosphamide, and paclitaxel (ECP) [21]. Patients with advanced resistant BC, who progressed after taxanes and anthracyclines had fewer treatment options and were frequently left with no viable medication of choice [22]. The use of liposomes as a carrier may dramatically minimize doxorubicin's cardiac toxicity. The best combination regimen based on liposomal pegylated doxorubicin (LPD) is currently being developed. As a result, methodically comparing and testing numerous combinations would be beneficial in generating the ideal combined regime based on LPD with Magnetothermy modification [23].

The aim to get and enhance the therapeutic benefits resulted from the synergetic effect from the combination of liposomal pegylated doxorubicin (LPD) and Magnetothermy (regional inductive mild hyperthermia) modification against advanced chemoresistant luminal B breast cancer to overcome several challenges, including side effects of anthracyclines, lower clinical tumor answer, limited stability.

2. Materials and methods

Patients included in this study had resistant Luminal B breast cancer and were inpatient at the State Non-commercial Enterprise “National Cancer Institute” of Ukraine during 2021 to 2023. The study was approved by the Regional Committee for Medical Research Ethics of SNE ‘National Cancer Institute’ (protocol 05.12.2020) and was performed under the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consents were obtained from patients prior to initiation of study procedures. Based on the safety and efficacy data for Liposomal Pegylated Doxorubicin (LPD), a study was proposed in which 60 patients advanced Luminal B1 breast cancer stabilization (by RECIST 1.1), e.g, chemoresistant; were randomized to receive one of the following two alternatives: **first** – intravenous infusion during sixty minutes liposomal

pegylated doxorubicin (LPD) 50 mg/m^2 and thirty minutes after drug infusion Local Magnetothermy during 30 minutes every four weeks – 4 cycles (30 patients); second group – AC (Doxorubicin 60 mg/m2 and Endoxan 600 mg/m2 and thirty minutes after drug infusion Local Magnetothermy during 30 minutes every two weeks (Dose-Dense therapy (DDT)) – 4 cycles every 14 day (30 patients). There were no episodes of LVEF reduction in any of the patients for research groups.

The following definitions were used to determine radiographic response: Complete regression (CR), a 30% decrease in the sum of the maximum diameters of the studied tumors (RECIST 1.1); partial regression (PR), a 30% decrease in the sum of the maximum diameters of the investigated tumors [24]. Index Ki67, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2/neu) expression immunohistochemistry was done on biopsy tissues using conventional procedures [25]. The therapeutic efficacy, toxicity, and side effects remain to be further analyzed and demonstrated.

Methods

Magnetothermy is a kind of inductive mild hyperthermia. The electric component varied between 70 and 1000 volts every minute, whereas the magnetic component varied between 0.5 and 16 ampers per minute. Irradiation was carried out for thirty minutes at a power output of 75 Watt and a frequency of 27.12±1.63 MegaHerz, with skin temperature monitoring in the electromagnetic field zone, which did not surpass 39°C. Magnetothermy (MT) (regional inductive moderate hyperthermia (RIMH)) was utilized to treat refractory breast cancer patients with an ECOG score of 0 to 2 who were eligible for liposomal chemotherapy. MagniTherm (Radmir, Kharkiv, Ukraine) carried out MT RIMH, in which electromagnetic fields were produced by the apparatus. The MagniTherm applicator was put near a breast cancer tumor - Figure 1 - to provide the most intense electromagnetic irradiation as assessed by the specific absorption rate (SAR) and temperature. Temperatures were kept under control with TM-4 fiber optical thermometers. Over 90% of individuals treated to electromagnetic irradiation did not experience a temperature increase of 39°C throughout the 30-minute treatment session. One of the hallmarks of magnetothermy is that the magnetic component of the electromagnetic field is recognized, as an important impact in induction heating and non-thermal effects on tumors using a frame applicator. The capacity of the human body to absorb magnetic component energy is limited. When compared to a magnetic field, the electric component is absorbed in greater amounts by the human body and causes hyperthermia to end at temperatures over 39 degrees Celsius. As a consequence, as compared to the action of electrical fields, the disadvantage of magnetic fields, which consists of the influence of minor induction heating, becomes a gain due to deep penetration into tissues with little distortion [26]. Magnetothermy with a frame applicator warms the tumor location more than fat because of the abundance of blood and lymphatic vessels. The applicator's electro-magnetic field has an electrical component that contributes to the therapeutic advantages.

Fever, systemic blood disease, metallic foreign substances in tissues, pregnancy, epilepsy, complicated ulcer, and mental disorder worsening were the principal contraindications of MT RIMH. In our investigation, MT RIMH was only utilized in conjunction with liposomal chemotherapy. COMSOL Multiphysics 5.4 program was utilized to predict the best distribution of electromagnetic and thermal fields for each patient - Figure 2 depicts the distribution of SAR estimated from the electric, magnetic, and thermal fields within the primary tumor. Figure 3 shows the highest values of SAR estimated from electric and magnetic fields, which were 0.02 and 3.39 W/kg, respectively.

3. Results and Discussion

Table 1 shows the clinical features of individuals in each group. The average age at the time of the initial diagnosis was 58.2±1.4 years. There were forty (66.67%) patients under the age of 60 and twenty (33.33%) patients above the age of sixty. There were no significant differences between the two groups in terms of age, tumor histology, tumor differentiation grade, tumor subtypes, distant metastases, or concurrent disorders. Eastern Cooperative Oncology Group (ECOG) - all patients 0-2. Concurrent disorders were present in 44 individuals, including the cardiovascular (23 patients), endocrine (8 patients), and gastrointestinal tract (13 patients). Ischemic heart disease, hypertensive heart disease, chronic cholecystitis, and pancreatitis were all common concomitant illnesses. Immunohistochemistry findings and tumor differentiation grade: GIII-IV in 36 cases and GI-II in 24 individuals. In all cases, the hormone receptor test indicated ER-positive and PR-negative tumors. All patients had HER-2/neu-negative tumors with Ki67 levels more than 30%. Nobody had distant metastases. Computed tomography and mammography were used to evaluate treatment outcomes. Complete regression was 3 (10.00%) for the first group and none for the second. Partial regression was performed on 19 (63.33%) patients in the first group and 18 (60.00%) patients in the second. Process stabilization was recorded in 8 (26.67%) of the cases, which was the same in both groups. Tumor progression was absent in the first group and evident in 4 (13.33%) in the second – Table 2.

Consequently, the overall efficacy of treatment for patients with resistant lum B1BC assigned to the first group was 73.33%, while in the second 60.00%. Combined MT RIMH and liposomal pegylated chemotherapy increased the overall efficacy of treatment by 13.33% ($\chi 2$=9.076; P<0.02). Picture 1 shows on axial CT scans for a 69-year-old female patient with resistant BC before and after treatment showed Partial regression. Computed tomography image analysis revealed, that there was a ∼ 54% reduction in primary tumor volume and edema after completing the combined treatment. No patient treated with LPD showed clinical symptoms of cardiotoxicity. Progression-free survival (PFS) after further surgery was similar (12.66 months in the LPD group versus 12.53 months in the dose-dense group) (HR 1.32; 95% CI, 0.94–1.72) – Figure 4. The objective response rate was similar: 16% for LPD versus 14% for the dose-dense arm.

Figure 1. *Typical arrangement of a patient with advanced breast cancer during a Magnetothermy session*

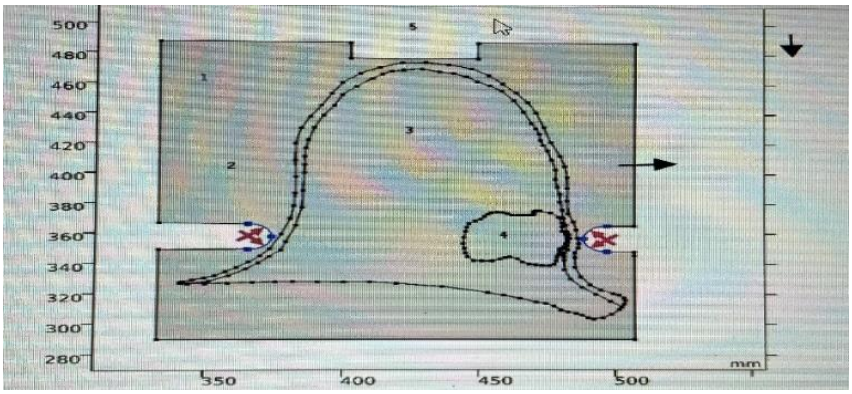


Figure 2. *The built model is shown for conducting hyperthermia:*
1 - air: 2 - skin; 3 – breast tissue; 4 – tumor; 5 – the applicator of the "MagniTherm" device

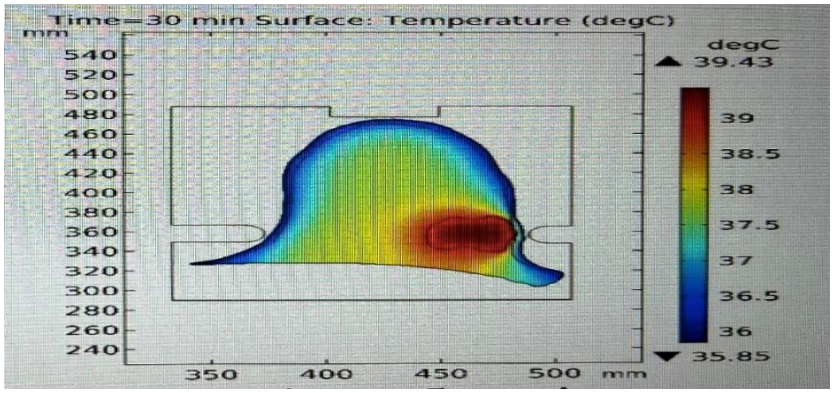


Figure 3. *Distribution of SAR calculated from the electric field (A), SAR calculated from the magnetic field (B), and temperature contour (C) in the prime tumor based on a computed tomography axial scan (axes in mm) for MagniTherm utilized with an output power of 75 W. 1 - indicates breast tissue; 2 – prime tumor*

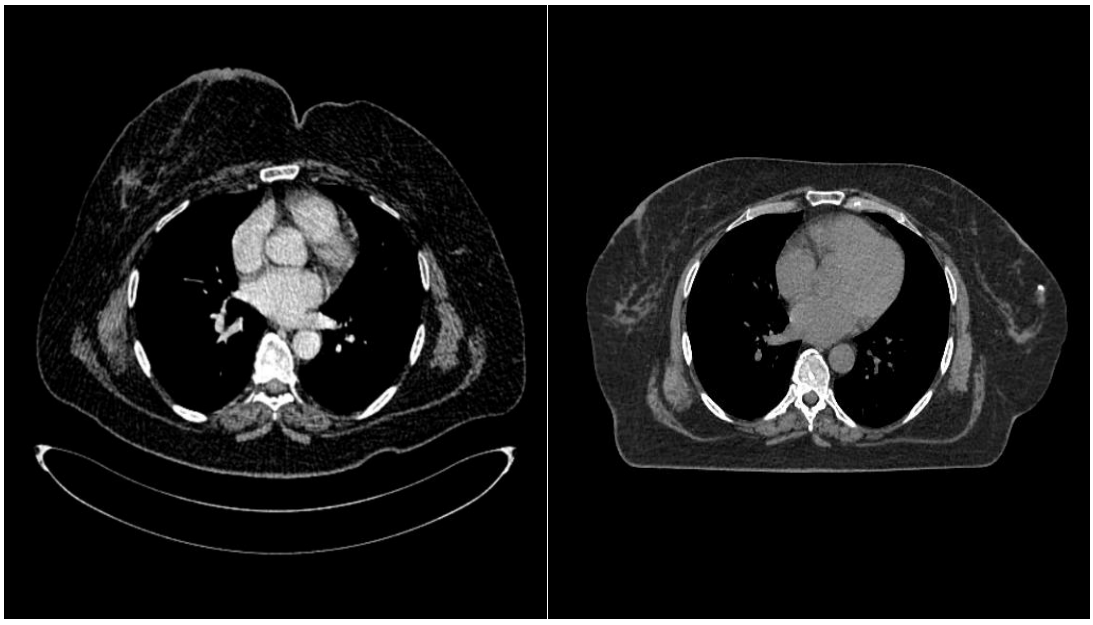
Table 1. Clinical characteristics

	First Group, n = 30 (%)	**Second Group, n = 30 (%)**	***p***
Age			
(30-44 years)	8 (26.67%)	7 (23.33%)	<0.05
(45-59 years)	10 (33.33%)	15 (50.00%)	
(60-74 years)	12 (40.00%)	8 (26.67%)	
Grade			<0.05
I-II	10 (33.33%)	14 (46.67%)	
III-IV	20 (66.67%)	16 (53.33%)	
Concomitant diseases			>0.05
Cardiovascular system	12 (40.00%)	11 (36.67%)	
Gastrointestinal tract	5 (16.67%)	8 (26.67%)	
Endocrine system	5 (16.67%)	3 (10.00%)	

Table 2. Treatment Results According to RECIST Criteria

Results	Patient Group, n (%)	
	first	second
Complete regression	3 (10.00%)	0
Partial regression	19 (63.33)	18 (60.00)
Stabilization	8 (26.67)	8 (26.67)
Progression	0	4 (13.33)

$p<0.05$



A **B**

Picture 1: *Axial CT scan for a 73-year-old female patient with resistant BC (1): (A) primary tumor volume before liposomal pegylated therapy and RIMH treatment 2.7 cm³ and (B) primary tumor volume after the combined treatment 1.46 cm³.*

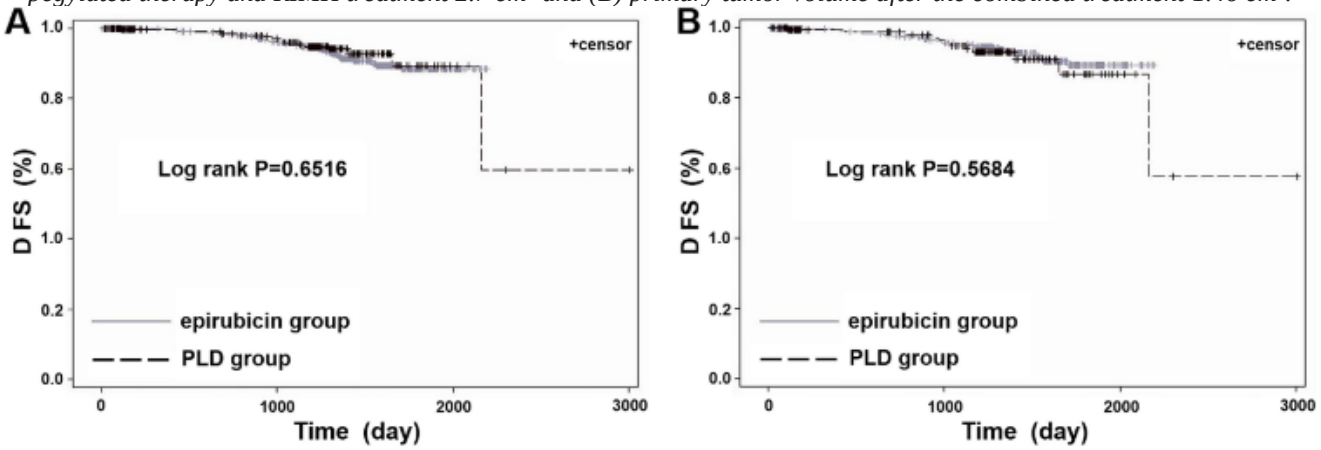


Figure 4. Kaplan-Meier curves of progression-free survival (PFS) of among patients who received **A**) LPD +MT; **B**) DDT+MT

Statistical analysis

The period from surgery to recurrence, metastasis, or death was referred to as progression-free survival (PFS). The incidence of adverse responses was the secondary result. To eliminate selection bias between the LPD+MT and DDT+MT groups, main features were assessed. Age, lymph node metastases, tumor size, and molecular type were the factors studied. All statistical tests were conducted on a two-sided basis with a significance threshold of = 0.05. The chi-square test or Fisher's exact test was used to compare the three-year PFS rate between the two groups. For the 3-year PFS rate difference, the 95% confidence interval (CI) was determined. A noninferiority test was carried out for exploratory reasons, with the noninferiority margin set at − 10% (on the basis of clinical considerations). Factors such as: 1) menopausal status (premenopausal or postmenopausal), 2) tumor size, e.g. characteristic of the advanced BC (T4a; T4в; T4c), 3) lymph node metastasis (N0, N1, N2), 4) clinical stage (IIB-IIIC), 5) ER status (positive or negative), 6) PR status (negative), 7) HER2 status (negative), 8) Ki-67 expression level (≥ 30%) were considered for the group analyses. The rate difference between the two groups and its 95% confidence interval was was − 0.33 [− 3.12, 1.89]. The lower limit of the 95% CI in the exploratory noninferiority analysis was − 5.0% > − 10.0%, indicating that the effectiveness of LPD+MT is not inferior to that of DDT+MT.

4. Discussion

Doxorubicin was the first anthracycline drug to be utilized in the treatment of breast cancer and is the most prevalent cardiotoxicity [27]. Because of its changed composition, liposome pegylated doxorubicin (LPD) has unique pharmacokinetic and pharmacodynamic features that can effectively restrict drug exposure in normal tissue and hence minimize toxicity while assuring therapeutic efficacy [28], so, when we can modificate this regimen, like in our study, with local Magnetothermy – results are inspiring: allows to increase by 15.34% the number of cases of complete and partial regression of the primary tumor according to the RECIST criteria; the method makes it possible to increase the percentage of organ-sparing surgeries by 11.74% and reconstructive-restorative surgeries by 11.55% [29]. The hottest temperature recorded on the field was 38.8°C. In the instance of the aforementioned, electromagnetic irradiation might have only resulted in moderate hyperthermia. MT RIMH is a more promising technique since temperatures over 42°C increase the formation of heat shock proteins in tumor cells, leading to chemotherapy resistance and hypoperfusion of the tumor and its environs. [30]. Thermotherapy is a therapy that tries to induce apoptosis without harming normal tissue due to variations in temperature tolerance between normal tissue and tumor cells by heating the human body systemically or locally using heat energy. In general, it aids in increasing the permeability of liposomes in tumor microvessels and facilitating drug accumulation in tumors [31]. Pathological complete response (pCR) is the primary efficacy result of neoadjuvant treatment for breast cancer. Previous research has found that the pCR of breast cancer patients following neoadjuvant chemotherapy ranges between 5-70% [32], 5-6% for luminal A cancer, 8-10% for luminal B cancer, 38% for HER2-positive cancer, and 23% for triple-negative cancer. [33]. The success of neoadjuvant treatment may be affected by clinical stage, HER2 status, Ki-67 expression, HR status, and other variables. LPD-containing neoadjuvant therapy has been found in several studies to be effective in the treatment of resistant breast cancer [34]. Fiegl M et al. [35] reported the findings of a noninferiority Phase III trial in which 509 patients with breast cancer were randomly assigned to receive LPD at a dosage of 50 mg/m^2 every 4 weeks (254 patients) or conventional doxorubicin at a dose of 60 mg/m^2 every 3 weeks (255 patients). The research accomplished its noninferiority goal, with PFS of 6.9 versus 7.8 months (HR 1.00; 95% CI 0.82-1.22). OS was equivalent with LPD and doxorubicin, at 21 and 22 months, respectively (HR 0.94; 95% CI 0.74-1.19). The objective response rate for LPD (33%) and doxorubicin (38%), was equally comparable. Surprisingly, the incidence of cardiotoxicity was much greater in the traditional doxorubicin group (HR 3.6; 95% CI 1.58-6.31): 48 patients (19.6%) treated with doxorubicin suffered cardiac toxicity compared to just 10patients in the LPD group (P=0.001). There were no patients in the LPD group who experienced clinical heart failure, whereas 10 patients (4%) in the standard doxorubicin arm developed clinical heart failure. To avert a

doxorubicin-related cardiac episode, seven individuals were treated with LPD. Furthermore, 16% of patients in the LPD arm got therapy for more than 9 months, compared to just 1% in the doxorubicin arm, and this was not associated with an increase in cardiac toxicity with LPD. In contrast, the prevalence of hand-foot syndrome was greater in the LPD group (48% versus 2%), that corresponds to our results, so combined MT RIMH and liposomal pegylated chemotherapy increased the overall efficacy of treatment by 13.33% ($\chi 2$=9.076; P<0.02). Yao L et al. found that in the treatment of locally advanced breast cancer, LPD-containing neoadjuvant chemotherapy was as more successful (22.9% pCR rate) as standard doxorubicin (14.4%) [36]. Dose-dense therapy (DDT) advantages - the phase 3 GIM2 trial (ClinicalTrials.gov Identifier:NCT00433420), 498 patients were treated with dose-dense ECP, 505 with dose-dense F-ECP, 528 with normal ECP, and 522 with standard F-ECP. The median DFS in the F-ECP group was 17 years after a median follow-up of 15 years and was not attained in the ECP group (unadjusted hazard ratio [HR], 1.09; 95% CI, 0.88-1.17; p=0.15). The predicted 15-year DFS rate in the F-ECP group was 54.3% and 58.7% in the ECP group. The median DFS in the F-ECP group was 17 years after a median follow-up of 15 years and was not attained in the ECP group (unadjusted hazard ratio [HR], 1.09; 95% CI, 0.88-1.17; P =0.15). The predicted 15-year DFS rate in the F-ECP group was 54.3% and 58.7% in the ECP group. The researchers wrote about it. "The long-term follow-up of the GIM2 trial continues to support the increased efficacy of a dose-dense schedule." [37].

DDT followed by CMF enhanced the 5-year RFS (75% vs. 69%, P = 0.0001) and 5-year OS rates (79% vs. 70%, P = 0.0004) of 1894 breast cancer patients following neo-adjuvant treatment [38].

In our investigation, we found similar outcomes: progression-free survival (PFS) after further surgery was similar (12.66 months in the LPD+MT group versus 12.53 months in the dose-dense+MT group) (HR 1.32; 95% CI, 0.94–1.72). Nonetheless, the follow-up period was just three years. The patients' progress is still being tracked, and the findings will be updated. When compared to other anthracyclines, LPD can significantly reduce the risk of cardiotoxicity, as shown Abrahams C and colleagues [39] - 756 cancer patients of whom 63.4% received anthracycline therapy – had different cardiotoxy, but with liposomal forms 33.7% of the patient's developed cardiotoxicity. LPD has been widely utilized to treat recurrent breast cancer, and its effectiveness has been well acknowledged. The study discovered that LPD combined with Magnetothermy can prolong progression-free survival (PFS) for breast cancer patients at pathological stages II-III, implying that it may be relevant to the different pathological phases of such cancer therapy. Our study looked at individuals with Lum B1 resistant breast cancer who were treated with LPD. At present research results suggest that it is effective for increasing the therapeutic efficacy of LPD combined with Magneothermy. In particular, the maximum tolerated dose of drugs could reach 240 mg PLD. In this study, we used a matched case-control design with stringent matching criteria to compare the effectiveness and safety of LPD in magnetothermic conditions vs. DDT+MT as next step after neoadjuvant chemotherapy AC-T, which patients were resistant in breast cancer patients, who received the treatment within the same period. The use of liposomal anthracyclines in combination with Local Magnetothermy in patients with advanced chemoresistant to standard regimens breast cancer is of particular interest, since this is presumably the subgroup who would benefit the most from anthracycline treatment.

This study also revealed that patients' pathological response rate was substantially related to thermal dosage, possibly because thermotherapy enhanced tumor vascular permeability and oxygen content, thereby playing a role in improving its therapeutic efficiency. The findings of this study revealed that combining MT RIMH with liposomal pegylated chemotherapy increased antitumor medication treatment effectiveness and quality of life in individuals with resistant BC. We suggest that future MT RIMH research should focus on creating neoadjuvant techniques for anti-resistant regulation of neoplasms.

5. Conclusions

- Liposomal anthracyclines have been demonstrated to be effective and safe in advanced chemoresistant Lum B breast cancer when combined with Magnetothermy (regional inductive mild hyperthermia).
- Adding Magnetothermy (regional inductive mild hyperthermia) to chemotherapy significantly improved response rate, progression-free survival, and overall survival.
- In the neoadjuvant therapy of breast cancer, the LPD-containing regimen+MT and DDT+MT regimens had comparable efficacy but differ in toxicity.

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