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LETROZOLE IMPROVES PROGRESSION-FREE SURVIVAL OF POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER TREATED WITH PEGYLATED LIPOSOMAL DOXORUBICIN AND MAGNETOTHERMY

Background. Resistance of the advanced breast cancer (aBC) to hormone therapy and chemotherapy due to hyperactivated PI3K-pathway caused by mutations in the *PIK3CA* gene is a major treatment problem. Combining pegylated liposomal doxorubicin (PLD) with mild magnetothermy (MT) and letrozole could improve the efficacy of treatment. The **aim** was to assess the effect of combined treatment with PLD, MT, and letrozole on the survival of patients with luminal B postmenopausal aBC with mutations in the *PIK3CA* gene. **Material and Methods.** The aBC postmenopausal patients who progressed on a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and an aromatase inhibitor (AI) or neoadjuvant chemotherapy (AC-T) were included in the study. Group 1 included 20 patients, treated with PLD + MT every 28 days (4 courses) and letrozole (daily per os, 4 months). Group 2 included 20 patients, who received the same treatment without letrozole. By *PIK3CA* status, each group included 10 patients with a mutant *PIK3CA* and 10 patients with a wild-type gene. **Results.** Application of PLD + MT in combination with letrozole demonstrated improved progression-free survival (PFS) compared to PLD + MT alone. In group 1, the median PFS was 10.6 months (95% CI, 7.4—11.9 months) compared to a median PFS of 8.9 months (95% CI, 6.1—9.7 months) in group 2 ($p = 0.005$). In the sensitivity analyses, PFS of patients with wild-type *PIK3CA* in the first cohort was 10.1 months (95% CI, 8.7—11.1 months) compared to 8.4 months (95% CI, 7.0—10.4 months) in groups 1 and 2 respectively ($p = 0.004$), by 1:1 greedy nearest neighbor matching. **Conclusion.** PLD with local MH in combination with letrozole was more effective irrespective of the *PIK3CA* gene status in postmenopausal aBC patients.

Keywords: advanced postmenopausal breast cancer, drug resistance, pegylated liposomal doxorubicin, mild magnetothermy, survival.

Despite the advancements in breast cancer (BC) treatment, chemotherapy improves the state of the majority of BC patients but exert limited efficacy due to the development of drug resistance [1, 2]. The drug resistance mechanisms play an important role in determining the first response to chemotherapy and influencing future outcomes. There are few mechanisms of chemoresistance that have been

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studied intensely. In particular, they are related to the mutations in residual cancer cells after neoadjuvant chemotherapy (NC) [3]. Also, one should mention the hyperactivated phosphatidylinositol-3-kinase (PI3K) pathway signaling caused by the mutations in the *PIK3CA* gene [4]. This gene encodes the alpha isoform of PI3K (p110α), and its mutations are present in approximately 40% of cases of HR^+, $HER2^-$ advanced BC (aBC) [5].

The detection of BC resistance to hormone therapy and chemotherapy is primarily based on the elevation of biomarkers such as *PIK3CA* and *ESR1* mutations and ALDH expression, whereas the identification of BC stem cells (CSCs) is primarily based on the upregulation of ALDH expression [6].

Recently, we have shown that pegylated liposomal doxorubicin (PLD) as a single agent is effective in patients with chemoresistant aBC with wild-type or mutant *PIK3CA* [7]. The triggered drug delivery systems have been found to increase drug accumulation in tumor lesions compared to free drug administration. Many studies have shown better targeting capabilities of cancer agents administered in thermosensitive liposomes [8].

Combination of a nanocomplex and local magnetotherapy (hyperthermy) has been found to enhance the growth inhibition of BC cells compared to the effects of the nanocomplex and officinal doxorubicin administered separately [9]. The advanced formulation technique in conjunction with mild hyperthermia has a high potential for the targeted delivery of cancer agents, improving their therapeutic efficacy [10].

The international expert recommendations suggest hormone therapy in combination with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6I) as the first-line treatment for patients with HR^+, $HER2^-$ aBC [11]. The addition of buparlisib or letrozole was more beneficial in the *PIK3CA* mutant BC cases compared to wild-type tumors [12]. A selective targeting of the specific PI3K-isoforms may have fewer side effects than PLD +MT (magnetothermy) with a broader PI3K inhibition. Several studies on the use of letrozole in combination with specific inhibitors of PI3K were reported [13].

Earlier, we have studied the efficacy of neoadjuvant chemotherapy in combination with regional MT for patients with locally aBC [14]. In this study, mild hyperthermia was used as a non-invasive, non-toxic method to enhance the efficacy and safety of PLD in combination with letrozole. We aimed to assess the effect of letrozole on the survival of patients with advanced luminal B postmenopausal BC with mutations in the *PIK3CA* gene, who were treated with PLD and MT.

This is the first study to investigate the feasibility of a combination program of liposomal anthracycline and MT, where letrozole was added as part of treatment for resistant postmenopausal BC.

Materials and Methods

This study was approved by the Ethics committee of the State Non-commercial Enterprise "National Cancer Institute of Ukraine" (December 12, 2023, № 249/2). The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The patient's consent regarding use of health-related data for research purposes was provided by all patients.

Forty postmenopausal aBC patients with the disease progression after CDK4/6i plus aromatase inhibitor or NC (doxorubicxin-cyclophosphamide followed by paclitaxel (AC-T) were included in the study. Group 1 included 20 patients treated with PLD (50 mg/m^2) + MT every 28 days (4 courses) and letrozole (every day per os, for 4 months). Group 2 included 20 patients who received PLD (50 mg/m^2) + MT every 28 days (4 courses), without letrozole. The regional inductive mild hyperthermia was administered 30 min after PLD + letrozole infusion. For MT, a MagTherm applicator (Radmir, Ukraine) was used as described in [14].

In each group (according to the gene mutation status), there were 10 patients with a mutant *PIK3CA* and 10 patients with a wild-type gene. The number of the previous lines of therapy did not serve as a baseline covariate for the group matching.

Patients were thoroughly examined. A complete blood count and blood chemistry tests were conducted. The instrumental investigation comprised a computed tomography (CT) scan, as well as an ECG and echocardiogram before the therapy, and a CT scan after 4 cycles of the combination therapy.

Progression-free survival (PFS) of the patients from both groups was estimated by the Kaplan — Meier method.

Progression or stabilization of the disease was defined according to Response Evaluation Criteria

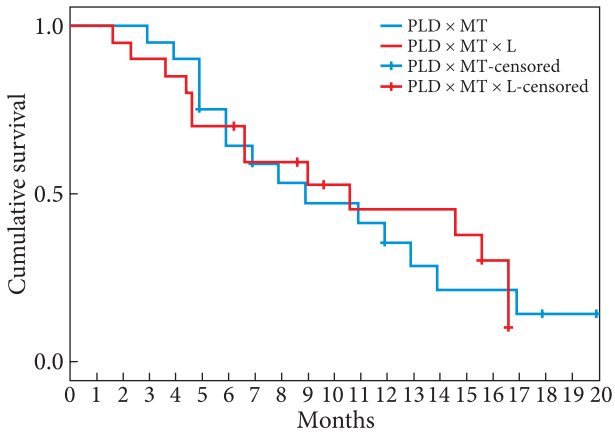

Fig. 1. Kaplan-Meier analysis of PFS of patients of groups 1 and 2

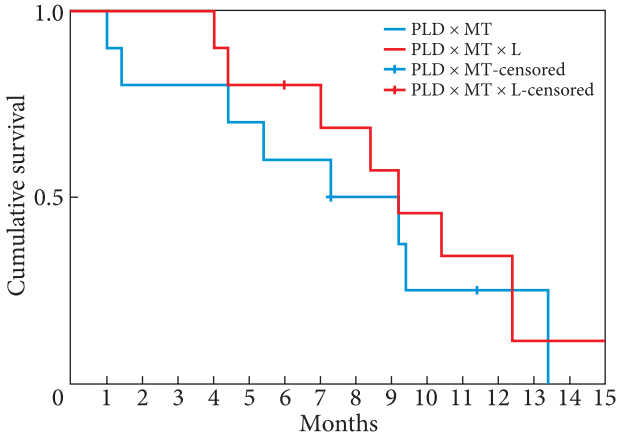

Fig. 2. PFS of patients of groups 1 and 2 with mutant *PIK-3CA*, odds weighting

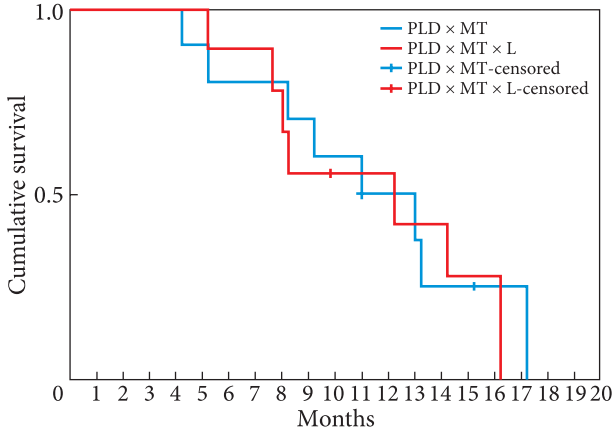

Fig. 3. PFS of patients of groups 1 and 2 with wild *PIK3CA* by odds, post-greedy nearest neighbor matching

In Solid Tumors (RECIST) v1.1, based on clinical and radiologic assessments.

The safety profile in this cohort was consistent with the known safety profile of PLD and MT, and absolutely comparable in both groups. Commonly experienced all-grade adverse events (AEs) were diarrhea, nausea, fatigue, decreased appetite, without other AE observed.

Results and Discussion

Overall, for all patients, PLD + MT combination with letrozole improved PFS in comparison with PLD + MT alone. Patients of group 1 had a median PFS of 10.6 months (95% CI, 7.4—11.9 months), while patients of group 2 had a median PFS of 8.9 months (95% CI, 6.1—9.7 months) ($p = 0.005$) (Fig. 1).

After the odds weighting, PFS of patients of group 1 with mutant *PIK3CA* was 9.2 months (95% CI, 7.2—10.0 months) vs 7.3 months (95% CI, 6.5—8.2 months) in patients of group 2 with mutant *PIK3CA* ($p = 0.004$) (Fig. 2).

In the sensitivity analyses using additional matching approaches, the PFS of patients of group 1 with wild-type *PIK3CA* was 10.1 months (95% CI, 8.7—11.1 months), compared with a median PFS of 8.4 months (95% CI, 7.0—10.4 months) of patients of group 2 with wild-type *PIK3CA* ($p = 0.004$), by 1 : 1 greedy nearest neighbor matching (Fig. 3).

Our study confirmed the efficacy and safety of PLD + MT with letrozole for the treatment of HR^+, $HER2^-$, *PIK3CA*-mutated drug resistant aBC.

Our results are in agreement with the data of other authors. In fact, in the study [15], the safety profiles and pharmacokinetics of PLD and officinal doxorubicin were similar while the toxicity in PLD was less pronounced [16], which supports clinical application of PLD in BC patients.

Earlier, we have studied the efficacy of NC in combination with MT for patients with locally aBC [14]. Chemotherapy combined with regional inductive moderate hyperthermia was also shown to be effective in patients with metastatic breast cancer [17].

In summary, our findings demonstrate that the use of PLD + MT in combination with letrozole in BC patients can reduce deleterious effects of doxorubicin therapy and improve their survival. On the premise of guaranteeing safety, subsequent studies may further explore optimal combined regimen of MT and PLD.

Conflict of interest

The authors claim no conflict of interest.

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ЛЕТРОЗОЛ ПОДОВЖУЄ ВИЖИВАНІСТЬ БЕЗ ПРОГРЕСУВАННЯ В ПОСТМЕНОПАУЗАЛЬНИХ ХВОРИХ НА РОЗПОВСЮДЖЕНИЙ РАК МОЛОЧНОЇ ЗАЛОЗИ ПРИ ТЕРАПІЇ ПЕГІЛЬОВАНИМ ЛІПОСОМАЛЬНИМ ДОКСОРУБІЦИНОМ У КОМПЛЕКСІ З МАГНІТОТЕРМІЄЮ

Стан питання. Резистентність розповсюдженого раку молочної залози (рРМЗ) до гормональної та хіміотерапії через гіперактивацію сигнального шляху PI3K внаслідок мутації гена *PIK3CA* становить серйозну проблему в лікуванні таких хворих. Поєднане застосування пегільованого ліпосомального доксорубіцину (ПЛД) з помірною магнітотермією (МТ) та летрозолом може покращати ефективність лікування. **Мета** роботи полягала у визначенні ефективності поєднаного застосування ПЛД та МТ з летрозолом у постменопаузальних хворих на рРМЗ люмінального В підтипу з мутаціями у гені *PIK3CA*. **Матеріали та методи**. В дослідження включали постменопаузальних хворих на рРМЗ з прогресуванням хвороби після проведеної терапії із застосуванням інгібітору циклін-залежної кінази 4/6 з інгібітором ароматази або неоад'ювантної хіміотерапії за схемою АС-Т. До групи 1 включили 20 хворих, які отримували ПЛД + МТ (4 курси раз на 28 днів) та летрозол (перорально щодня впродовж 4 місяців). До групи 2 включили 20 хворих, які отримували ту ж терапію, що в групі 1, але без додавання летрозолу. У кожній групі було 10 хворих з мутованим *PIK3CA* та 10 хворих з геном дикого типу. **Результати**. При застосуванні ПЛД + МТ у поєднанні з летрозолом виявлено покращання показників виживаності без прогресування (ВБП). Медіана ВБП у групі 1 складала 10,6 місяців (95% ДІ 7,4—11,9 місяців), а в групі 2 — 8,9 місяців (95% ДІ 6,1—9,7 місяців) (p = 0,005). Аналіз чутливості показав, що у хворих з *PIK3CA* дикого типу групи 1 медіана ВБП складала 10,1 місяців (95% ДІ, 8,7—11,1 місяців) у порівнянні з 8,4 місяцями (95% ДІ, 7,0—10,4 місяців) у групі 2 (p = 0,004). **Висновки**. Схема ПЛД з локальною МТ в поєднанні з летрозолом у постменопаузальних хворих на рРМЗ є більш ефективною, ніж без застосування летрозолу, незалежно від статусу гена *PIK3CA*.

Ключові слова: розповсюджений рак молочної залози, лікарська резистентність, пегільований ліпосомальний доксорубіцин, помірна магнітотермія, виживаність.