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USE OF CYCLIN-DEPENDENT KINASE 4 AND 6 INHIBITORS IN TREATING METASTATIC BREAST CANCER – A YEAR-LONG EXPERIENCE OF SUBOTICA GENERAL HOSPITAL IN PATIENT FOLLOW-UP

PRIMENA INHIBITORA CIKLIN-ZAVISNIH KINAZA 4 I 6 U LEČENJU METASTATSKOG KARCINOMA DOJKE – JEDNOGODIŠNJE ISKUSTVO U PRAĆENJU PACIJENATA OPŠTE BOLNICE SUBOTICA

Teodora BRDAR ZELEN, Marija JOVIŠEVIĆ and Anja PRICA

Summary

Introduction. According to GLOBOCAN data from 2020, breast cancer ranks first in the number of newly diagnosed malignancies. The treatment of advanced, hormone-positive breast cancer has evolved with the use of cyclin-dependent kinase 4 and 6 inhibitors in first- and second-line treatment for metastatic, hormone-positive, HER2-negative breast cancers, in combination with endocrine therapy. As of May 31, 2022, these drugs have become available in the Republic of Serbia. This paper aims to present a one-year experience of a secondary health center in monitoring patients using the treatments. **Material and Methods.** The data analysis included patients treated with cyclin-dependent kinase 4 and 6 inhibitors from June 1, 2022, to June 1, 2023, at General Hospital Subotica. The analysis covered demographic data, disease presentation, previous therapies, drug usage, side effects, duration, and therapy outcomes. Patients were categorized into two groups based on age (<60 and >60 years) and by the nature of their disease (relapsed or initially metastatic). **Results.** A total of 43 patients were treated with cyclin-dependent kinase 4 and 6 inhibitors: 23 (53.5%) in the first line and 20 (46.5%) in the second line. The median therapy duration was eight cycles for patients younger than 60 years. A good therapeutic response was observed in 53.5% of patients. Patients younger than 60 years with late relapse exhibited statistically significantly better treatment outcomes compared to those older than 60 years (p=0.04). The most common site of metastases was the bones (51%, 22 patients), with half of these patients showing a good therapeutic response. **Conclusion.** Although the observed period is short, ongoing monitoring and further research are planned to share experiences on the use of these drugs.

Key words: Breast Neoplasms; Neoplasm Metastasis; Cyclin-Dependent Kinase Inhibitor Proteins; Antineoplastic Agents, Hormonal; Treatment Outcome

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Sažetak

Uvod. Prema podacima GLOBOCAN iz 2020. godine, karcinom dojke je prvi po broju novodijagnostikovanih slučajeva i čini 11,7% svih maligniteta. Lečenje uznapredovalog, hormonpozitivnog karcinoma dojke je promenjeno primenom inhibitora ciklin-zavisnih kinaza 4 i 6 u prvoj i drugoj liniji metastatskih, hormon-pozitivnih, Her2 negativnih karcinoma dojke u kombinaciji sa endokrinom terapijom. Od 31. 5. 2022. godine ovi lekovi su dostupni u Republici Srbiji. Cilj rada je prikazivanje jednogodišnjeg iskustva sekundarnog zdravstvenog centra u praćenju pacijenata koji ih koriste. **Materijal i metode.** Analiza podataka obuhvatila je pacijente lečene inhibitorima ciklin-zavisnih kinaza 4 i 6 u periodu od 1. 6. 2022. do 1. 6. 2023. godine u Opštoj bolnici Subotica. Analizirani su demografski podaci, prezentacija bolesti, prethodna terapija, primena navedenih lekova, neželjena dejstva, dužina trajanja i ishod terapije. Pacijente smo podelili prema starosti u dve grupe (< 60 i > 60 godina), a potom i u odnosu na relaps ili inicijalno metastatsku bolest. **Rezultati.** Ukupno 43 pacijenta su lečena inhibitorima ciklin-zavisnih kinaza 4 i 6; u prvoj liniji njih 23 (53,5%), a u drugoj 20 (46,5%) pacijenata. Medijana dužine trajanja terapije od osam ciklusa zabeležena je kod pacijenata mlađih od 60 godina. Dobar terapijski odgovor zabeležen je kod 53,5% pacijenata. Pacijenti mlađi od 60 godina sa kasnim relapsom imaju statistički značajno bolje ishode lečenja u poređenju sa pacijentima starijim od 60 godina (p = 0,04). Najučestalija lokalizacija metastaza su kosti (51%, 22 pacijenta); polovina ovih pacijenata ima dobar terapijski odgovor. **Zaključak.** Posmatrani period je kratak te se planira dalje praćenje i istraživanje u cilju razmene iskustava o primeni ovih lekova.

Ključne reči: karcinom dojke; metastaze; inhibitori ciklin zavisne kinaze; hormonska antineoplastična terapija; ishod lečenja

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Introduction

According to the 2020 Global Cancer Statistics (GLOBOCAN), breast cancer has surpassed lung cancer in terms of the number of newly diagnosed cases, with 2.3 million new cases, accounting for 11.7% of all malignancies. Breast cancer also ranks first in mortality among women [1]. In 2021, approximately 4,500

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Abbreviations

HR+	– hormone receptor positive
ER	– estrogen receptor
PgR	– progesterone receptor
Her2	– human epidermal growth factor 2
DFS	– disease free survival
CDK4/6 inhibitors	– cyclin dependent kinase 4 and 6
PFS	– progression free survival
iDFS	– invasive disease free survival
RFZO	– Republic Health Insurance Fund
AI	– aromatase inhibitors
CTCAE	– Common Terminology Criteria for Adverse Events
CR	– complete response
PR	– partial response
SD	– stabile disease
PD	– progressive disease

new cases of breast cancer were diagnosed in the Republic of Serbia, making it is the most frequent malignancy among women in the country [2]. **Figure 1** illustrates the global distribution of similar cases.

Hormone-positive breast cancer constitutes about 75% of all breast cancer cases [3]. Patients with hormone receptor-positive (HR+) breast cancer, characterized by estrogen receptor (ER) and progesterone receptor (PgR) positivity, generally have better survival rates compared to other types of breast cancer, such as triple-negative or HER2-positive breast cancer. This improved survival is largely due to the effective use of endocrine therapy, which is employed in neoadjuvant, adjuvant, and metastatic stages of the disease. Adjuvant endocrine therapy can reduce the risk of disease relapse by approximately 50% [4]. However, there remains a risk of relapse even after a prolonged disease free survival (DFS) period. Consequently, diagnostic tests such as OncotypeDX and Mammaprint have been developed to predict which patients at a higher risk of relapse and to aid in the decision-making process regarding adjuvant chemotherapy [5].

Despite advancements in early detection and treatment of breast cancer, which have led to decreased mortality rates, there is still a need for new treatment methods and the identification of new predictive and prognostic factors [6].

Figure 1. Most commonly diagnosed malignant disease per country
Slika 1*. Najčešće dijagnostikovano maligno oboljenje u zemljama sveta*

The treatment landscape for advanced, hormone-positive breast cancer has undergone significant changes following the PALOMA-2, MONALEESA-2, MONALEESA-7, and MONARCH-3 studies. These studies led to the approval of palbociclib, ribociclib, and abemaciclib for first-line use in metastatic, hormone-positive, HER-2 negative breast cancer in combination with endocrine therapy. These drugs are CDK4/6 inhibitors that work by inhibiting the transition of cells from the G1 phase to the S phase of the cell cycle [7].

The PALOMA-3, MONARCH-2, and MONALEESA-3 studies are placebo-controlled, randomized phase III trials that investigated the efficacy of CDK4/6 inhibitors in combination with fulvestrant in postmenopausal women who had progressed on previous endocrine therapy. All these studies demonstrated a significant prolongation of progression free survival (PFS) [8]. Encouraged by the results in metastatic disease, researchers have also explored the effect of these drugs in the earlier stages of the disease. However, the PALLAS and PENELOPE B studies, which examined the adjuvant use of palbociclib in combination with endocrine therapy, did not show a significant prolongation of invasive disease free survival (iDFS) compared to adjuvant endocrine therapy alone, and thus, these drugs have not been adopted for adjuvant treatment [9]. Conversely, abemaciclib was approved for adjuvant use with endocrine therapy following the results of the monarchE study in October 2021 [10].

Ongoing studies continue to investigate the use of CDK4/6 inhibitors across various stages of the disease, in combination with different endocrine therapies, and alongside anti-HER2 therapy in HR+/HER2-positive breast cancers [11].

As of May 31, 2022, in the Republic of Serbia, the Republic Health Insurance Fund (RFZO) has approved the use of CDK4/6 inhibitors, specifically palbociclib and ribociclib, for the treatment of hormone receptor-positive and HER2-negative advanced or metastatic breast cancer. These drugs can be used as initial endocrine therapy in combination with an aromatase inhibitor (AI) or in the second line in combination with fulvestrant for patients who have previously received endocrine therapy. The decision to use these drugs is made by three doctors in tertiary health institutions where the medications are dispensed [12].

Material and Methods

To present a one-year experience in the follow-up of patients who received CDK4/6 inhibitors at the oncology center, patient data were collected using the electronic hospital information system and analyzed using Microsoft Excel. The research was approved by the ethics committee of the Subotica General Hospital. The observation period spanned from June 1, 2022 to June 1, 2023.

The data analysis encompassed demographic characteristics, previous treatments, application of CDK4/6 inhibitors, side effects according to the Common Terminology Criteria for Adverse Events (CTCAE), and duration of therapy. Disease outcomes were assessed

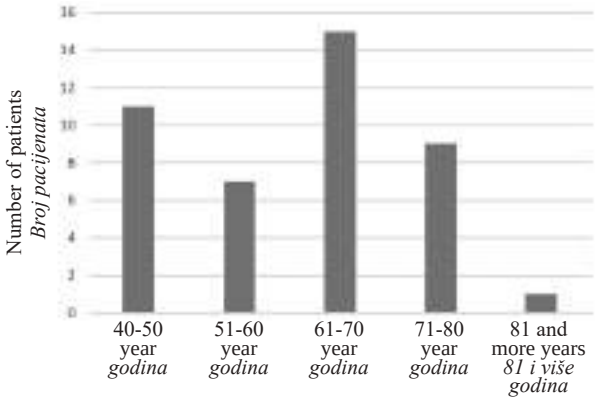
based on clinical, radiological, and laboratory findings and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The results were presented in tabular and graphical formats, and statistical processing included the application of the Chi-square test.

The study utilized sources from verified professional literature on established knowledge about hormone-positive breast cancer and its treatment, as well as data from recent research studies, scientific works, and international guidelines. This approach aimed to unify and compare these sources with our own experience.

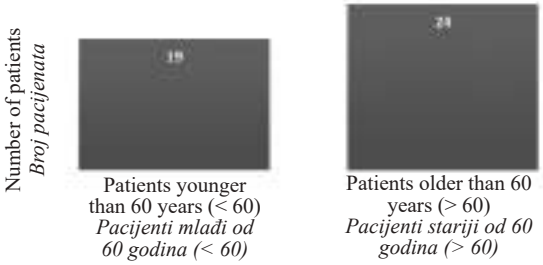
Results

During the observed period, 43 patients treated with CDK4/6 inhibitors under the new RFZO indication were monitored at Subotica General Hospital. Among these patients, one was male, and 42 were female. The median age was 62 years, ranging from 40 to 84 years. The age distribution of patients is illustrated in **Graph 1,** which divides them into two groups: those younger than 60 years (<60) and those older than 60 years (>60) **(Graph 2).**

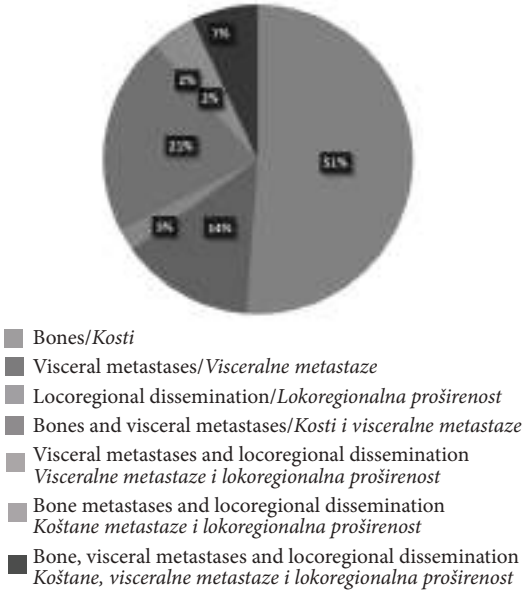
Out of the total number of patients, 29 (67.4%) experienced a relapse of the disease, while 14 (32.6%) were initially diagnosed and treated as having metastatic disease. An early relapse was noted in 16 (37.2%) patients, whereas 13 (30.2%) had a late relapse.



Graph 1. Age structure of patients treated with CDK4/6 inhibitors
Grafikon 1. *Starosna struktura pacijenata lečenih CDK4/6 inhibitorima*



Graph 2. Groups of patients according to age
Grafikon 2. *Grupe pacijenata prema godinama starosti*



Graph 3. Metastatic sites and their frequency
Grafikon 3. *Lokalizacije metastaza i njihova zastupljenost*

Graph 3 shows the localization of metastases, revealing that bone metastases were the most common, occurring in 22 patients (51%). Tamoxifen and anastrozole were the most frequently used adjuvant therapies among our patients.

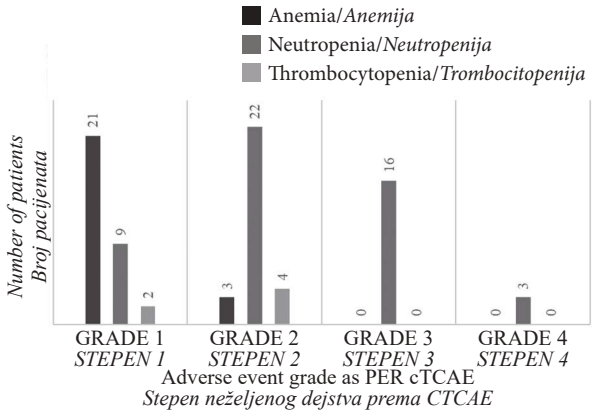
In the first line of metastatic disease, an aromatase inhibitor (anastrozole or letrozole) was used as monotherapy by 10 patients. CDK4/6 inhibitors were not initially represented in Serbia. Twelve patients in each group received chemotherapy and/or palliative radiation for metastatic disease, and of the 12 patients with bone metastases, 10 (83.3%) began treatment of advanced disease with chemotherapy.

In the first line of metastatic disease, 23 patients (53.5%) were treated with CDK4/6 inhibitors, while 20 patients (46.5%) received this therapy as a second line. The patients were nearly evenly split between ribociclib (21 patients, 48.8%) and palbociclib (22 patients, 51.2%). In combination with CDK4/6 inhibitors, aromatase inhibitors were used in 23 patients (53.5%) for first-line treatment, and fulvestrant was used in 20 patients (46.5%) for second-line treatment).

The duration of therapy expressed in months (cycles) was from 4 to 12. In the first line of treatment, the median duration was 7 cycles, while in the second line, it was 6 cycle. Patients younger than 60 years had a median duration of therapy of 8 cycles, longer in the first line (8 cycles) compared to the second line (6 cycles).

Hematological toxicity was the most common side effect **(Graph 4).**

Grade II neutropenia occurred in 22 patients (51.2%), while anemia, present in 21 patients (48.8%), was grade I, and no patients required blood transfusion. Hepatotoxicity was observed in 3 patients (9.3%), manifesting as elevated liver aminotransferases or transaminases, with values tripled



Graph 4. Frequency of hematological toxicity during CDK4/6 inhibitors treatment
Grafikon 4*. Zastupljenost hematološke toksičnosti kod primene CDK4/6 inhibitora*

in 2 patients and quadrupled in 1 patient. After recommended symptomatic therapy, the values returned to acceptable ranges, allowing therapy continuation without further complications. Cardiac toxicity, manifested by QTc interval prolongation, was recorded in 2 patients (4.6%). Due to side effects, the drug dose was reduced for the first time in 9 patients (21%) and for the second time in 2 patients (4.6%), while in 2 patients, the treatment was initiated at a lower dose of CDK4/6 inhibitors due to age and comorbidities. Adverse drug reactions did not lead to therapy discontinuation.

A good therapeutic response (CR, PR and SD) was recorded in 23 patients (53.5%). A complete response to therapy was noted in two patients younger than 60 years. Treatment outcomes by patient groups, in relation to early or late relapse or initially metastatic disease, are shown in **Table 1.** Patients younger than 60 years with late relapse had statistically significantly better treatment outcomes compared to patients older than 60 years (p=0.04). Patients with bone metastases had a good therapeutic response in 50% of cases. Those with bone metastases combined with other metastasis localizations had a good therapeutic response in 54% of cases.

The localization of metastases, line of treatment, and reduction of the drug dose did not have a statistically significant effect on the treatment outcomes with CDK4/6 inhibitors in our patients.

Discussion

In recent years, numerous studies have evaluated the use of CDK4/6 inhibitors in clinical practice, comparing the results with randomized clinical trials that lead to their approval for breast cancer treatment. A study conducted in Brazil included 67.6% of patients disease relapse, and 55.6% received a CKD4/6 inhibitor as first-line treatment for metastatic disease. The most common site of metastases was the bones, in 83.8% of cases, similar to our data [13].

In Germany, after CDK4/6 inhibitors became available, the use of chemotherapy decreased from 42% to 27% over two years [14]. According to our data, a large number of patients still initiated treatment with chemotherapy for metastatic disease, even in the absence of a visceral crisis.

In the study by Knudsen et al., letrozole was the predominant endocrine therapy used, with other aromatise inhibitors (AIs) being less common [15]. In contrast, anastrozole was the first choice of AIs for our patients. Our data indicate that both available CDK4/6 inhibitors, ribociclib and palbociclib, were equally used, whereas in a study conducted in four centers in Germany, approximately 72% of patients used palbociclib. Germany recommendations from 2021, based on data from the MONALEESA-7 study, favor ribociclib for premenopausal patients when combined with AI [16]. The Hellenic Cooperative Oncology Group reported that 82.5% of patients were treated with palbociclib in combination with endocrine therapy [17], and researchers from Asia shared that 95% of their patients were treated with palbociclib [18].

In a multicenter German study, the dose of the drug was reduced in about 20% of patients, with hematological toxicity, primarily neutropenia, being the most common side effect is [16]. Our data also similarly showed hematological toxicity as the prime side effect.

Table 1. Treatment outcomes
Tabela 1. *Ishodi lečenja pacijenata*

Patient group *Grupa pacijenata*	Treatment outcome/*Ishod lečenja*				
	CR	PR	SD	PD	∑ N
Early relapse < 60/*Rani relaps < 60 N*	0	2	3	5	10
Early relapse > 60/*Rani relaps < 60 N*	0	1	2	3	6
Late relapse < 60*/*Kasni relaps < 60* N*	2	3	1	0	6
Late relapse > 60*/*Kasni realps > 60* N*	0	1	1	5	7
Initially metastatic < 60/*Inicijalno metastatski < 60 N*	0	0	1	2	3
Initially metastatic > 60/*Inicijalno metastatski > 60 N*	0	5	1	5	11
∑ N	2	12	9	20	43

N – number of patients/*N – broj pacijenata*
* p=0.04

In an Asian study, almost 50% of patients required a dose reduction, which did not affect PFS [18]. In Brazil, nearly half of the patients required dose reduction due to side effects, mainly grade III or IV neutropenia [13]. According to our experience, CDK4/6 inhibitors proved to be quite safe, and a systematic review of the literature indicates preservation of the quality of life and positive trend in pain control, similar to when applying only endocrine therapy [19]. Fradley et al. showed that cardiovascular side effects occur in a quarter of patients [20], suggesting the need for more intensive monitoring of cardiovascular function in patients treated with CDK4/6 inhibitors.

Nadia Harbeck and colleagues conducted a systematic review of literature published in the period from 2015 to 2019 on the use of CDK4/6 inhibitors in treating metastatic, hormone-positive breast cancer. The majority of studies (79 out of 114) included patients treated with palbociclib, with approximately half of the studies conducted in the United States. The mean or median follow-up in studies reporting PFS and OS ranged from 6 to 24.4 months. Median PFS was 13.3 months with the use of AI and palbociclib, and 5.8 months with the use of palbociclib and fulvestrant. Most patients who had stable disease after six months of treatment were those treated with palbociclib and AI, regardless of the therapy line [21]. Our data similarly indicate that stable disease or progression occurs at similar rates, irrespective of the choice of CDK4/6 inhibitor and endocrine therapy.

In one study, the mean treatment with ribociclib and AI in any treatment line was 4.2 months [22]. The median treatment duration in studies ranges from 1.8 to 19 months for ribociclib + AI, and 3.9 to 15.8 months for palbociclib + AI [21].

In all lines of treatment, in the Brazilian study found that patients treated with ribociclib had the longest PFS (28 months), a statistically significant difference compared to those treated with palbociclib (14 months) and abemaciclib (6 months) (p=0.002). No statistically significant difference was observed in the first line of treatment [13]. This is one of the few studies comparing individual CDK4/6 inhibitors, indicating a need for more such studies to provide clearer insights.

Conclusion

We are confident in the continued use of both drugs equally in treating metastatic, hormone-positive breast cancer. It is imperative to reduce and limit the use of chemotherapy in favor of these targeted therapies. The use of CDK4/6 inhibitors has proven to be safe, and we have gained sufficient confidence in managing their side effects. However, the observed period in our study is relatively short. Thus, ongoing monitoring and exchange of experiences are necessary to ensure optimal treatment and care for patients.

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