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Perspectives on the Clinical Implications and Quality of Life in Patients with HR+/HER2− Breast Cancer Undergoing Treatment with CDK4/6 Inhibitors

PhD THESIS ABSTRACT

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Rationale for Choosing the Research Topic

The rationale for selecting the research topic entitled *"Perspectives on the Clinical Implications and Quality of Life in Patients with HR+/HER2− Breast Cancer Undergoing Treatment with CDK4/6 Inhibitors"* stems from the pressing need to deepen our understanding of the balance between therapeutic efficacy and the long-term impact on quality of life in this particular patient population. In the context of recent advances in targeted therapy for hormone receptor-positive breast cancer, CDK4/6 inhibitors have emerged as pivotal components in the therapeutic strategy for HR+/HER2− metastatic disease, demonstrating significant benefits in terms of progression-free survival (PFS) and overall survival (OS). Nevertheless, numerous challenges persist regarding the heterogeneity of response, the development of secondary resistance, the management of the toxicological profile, and, not least, the influence of treatment on patients' functional status, psychosocial well-being, and quality of life. The choice of this research topic reflects an ongoing commitment to patient-centered medicine and to the integration of clinical and humanistic dimensions into modern oncologic practice, with the aim of contributing to the personalization and optimization of the therapeutic trajectory in breast cancer.

Relevance, Novelty, and Timeliness of the Research Topic

The importance, novelty, and timeliness of the topic addressed in this doctoral thesis derive from the convergence of several key directions in contemporary oncology: the advancement of molecular targeted therapies, the need to refine patient selection criteria, and the integration of quality of life measures into the assessment of therapeutic success. CDK4/6 inhibitors have revolutionized the treatment landscape of advanced HR+/HER2− breast cancer, shifting the therapeutic paradigm and offering improved prognoses for a broad subgroup of patients. However, their implementation in clinical practice brings forth significant challenges, including the identification of predictive biomarkers of response, the management of hematologic and non-hematologic toxicities, and the evaluation of treatment impact on quality of life. In a medical context increasingly focused not only on prolonging survival but also on maintaining an active and dignified life, this research addresses a current and pressing need. By exploring the clinical implications and the impact on quality of life, the topic aligns with the trend toward personalized oncology and contributes to the development of an integrative perspective, oriented toward outcomes that are both medically and humanistically meaningful.

Working Hypothesis

The working hypothesis of the present thesis is based on the premise that treatment with CDK4/6 inhibitors in combination with endocrine therapy not only improves clinical parameters of therapeutic efficacy in patients with HR+/HER2− breast cancer but also has a significant impact on quality of life, influencing their functional, psychological, and social status in a multidimensional manner. It is assumed that, despite the evident oncologic benefits, the toxicity profile of these agents and the prolonged duration of treatment may generate a subjective burden that must be evaluated and correlated with objective clinical data in order to provide a holistic assessment of therapeutic efficiency. Consequently, the integration of quality-of-life evaluation in the analysis of therapeutic response will highlight meaningful differences among patient subgroups, offering a solid foundation for personalized treatment strategies and optimized clinical decision-making.

General Objectives

The overarching objectives of this thesis aim for an integrative and multidimensional approach to the impact of CDK4/6 inhibitor therapy on patients diagnosed with HR+/HER2− breast cancer, with the ultimate goal of substantiating patient-centered, personalized therapeutic strategies. The study seeks to evaluate the clinical benefits of this therapeutic approach by analyzing overall survival (OS) and progression-free survival (PFS) in correlation with clinico-biological variables and the type of inhibitor used, as well as the influence of comorbidities on treatment efficacy and tolerability. Another major objective is to identify the predominant symptoms affecting quality of life, with a focus on frequent and agent-specific adverse effects such as fatigue, sleep disturbances, pain, and gastrointestinal symptoms. Additionally, the study aims to compare the impact of different CDK4/6 inhibitors on physical, social, and emotional functioning, and to analyze the relationship between certain clinico-pathological characteristics (histological grade, metastatic status, lymph node involvement) and the subjective perception of health status. Special attention is also given to psychological symptoms such as depression, anxiety, and stress, exploring their role in treatment adherence and oncologic outcomes. Ultimately, based on the obtained results, the research intends to formulate recommendations aimed at optimizing the medical and psychosocial care of patients, with a view toward

improving treatment tolerability, compliance, and quality of life in the current oncological context.

Metastatic Breast Cancer: Epidemiological and Therapeutic Context

Metastatic breast cancer represents a major global public health challenge, accounting for a significant proportion of cancer-related mortality among women. The subtype characterized by hormone receptor positivity and HER2 negativity (HR+/HER2−) is the most frequently encountered, comprising approximately 70% of all breast cancer cases. This high prevalence has important implications for therapeutic strategies and patient prognosis (1).

According to the GLOBOCAN 2022 estimates, approximately 2.3 million new breast cancer cases were diagnosed worldwide among women, representing 11.5% of all cancer cases. Breast cancer accounted for approximately 6.9% of all cancer-related deaths in women, ranking fifth globally in cancer mortality (2). In Europe, breast cancer is the most common malignancy among women, with an age-standardized incidence of 74.3 per 100,000 women. Breast cancer-related mortality was reported at 16.1 per 100,000 women in Europe and 12.7 per 100,000 women in North America (2).

In Romania, breast cancer ranks as the second most common malignancy across both sexes, following colorectal cancer, with 12,685 new cases reported in 2022, representing 12.1% of all female cancer cases. Breast cancer-related mortality in Romania reached 3,877 deaths in 2022, accounting for 6.9% of all female cancer deaths (2).

Current systemic treatment for metastatic HR+/HER2− breast cancer includes endocrine therapy, targeted agents, and chemotherapy. A major advancement in the management of this disease subtype is represented by cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), with three agents currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA): palbociclib, ribociclib, and abemaciclib.

The following chapters synthesize the existing data on:

- the mechanism of action of these agents,
- their pharmacodynamic profiles and toxicity differences,
- potential mechanisms of resistance and the role of biomarkers,

- evidence regarding cost-effectiveness and tolerability,
- quality of life (QoL) considerations in patients with breast cancer.

Chapter 1 provides a general overview of CDK4/6 inhibitors in the treatment of metastatic HR+/HER2− breast cancer. This chapter is structured into eight subsections:

1. Introduction to metastatic HR+/HER2− breast cancer
2. The role of the cell cycle in oncogenesis and the involvement of CDK4/6
3. Key mechanisms of resistance and biomarkers
4. Endocrine therapy resistance and sensitivity to CDK4/6 inhibitors – a noteworthy association
5. CDK4/6 inhibitors – a landmark in the treatment of metastatic HR+/HER2− breast cancer
6. Primary and acquired resistance to CDK4/6 inhibitors
7. Lack of prospective randomized data for second-line treatment
8. Conclusions

The conclusions synthesized from the literature review conducted in this first chapter underscore the current complexity of HR+/HER2− breast cancer treatment and highlight the urgent need for personalized therapeutic approaches in the absence of clinically validated molecular biomarkers to guide standardized treatment selection. Although no molecular predictor of response to CDK4/6 inhibitors has yet been approved, recent advances in genomic profiling technologies and emerging data from translational studies offer promising perspectives for individualized therapeutic decision-making. Optimal management of metastatic disease becomes critical in the context of limited access to subsequent lines of therapy and the major impact of first-line treatment choice on overall survival.

In this regard, the systematic exploration of new molecular targets and the evaluation of resistance mechanisms—such as retinoblastoma protein (pRb) loss, activation of the PI3K/AKT/mTOR pathway, or the Cyclin E–CDK2 axis—should be integrated into clinical decision algorithms. The validation and application of proposed biomarkers through advanced

techniques such as whole-genome sequencing and liquid biopsy may significantly contribute to optimizing treatment selection and improving therapeutic efficacy based on the molecular profile of each patient.

Chapter 2 of this thesis addresses the clinical applications, current challenges, and future perspectives related to the use of CDK4/6 inhibitors and is structured into seven subsections:

1. Results from Phase III clinical trials (PALOMA, MONALEESA, MONARCH)
2. Tolerability and management of CDK4/6 inhibitor-related adverse events
3. Comparative analysis of toxicity profiles
4. Efficacy of CDK4/6 inhibitors in the context of visceral crisis
5. Cost-effectiveness considerations and the SONIA trial
6. Evaluation of adverse event frequency
7. Quality of life considerations in breast cancer patients

The consolidated conclusions from the pivotal Phase III clinical trials—PALOMA, MONALEESA, and MONARCH—strongly support that the addition of CDK4/6 inhibitors to endocrine therapy leads to a significant improvement in progression-free survival (PFS) and a meaningful benefit in overall survival (OS), thereby validating the integration of these agents into the first-line treatment of patients with advanced HR+/HER2− breast cancer. This represents a major shift in the therapeutic standard for this disease.

Although CDK4/6 inhibitors have a generally favorable safety profile and are well tolerated in clinical practice, the emergence of adverse events—particularly hematologic and gastrointestinal—requires close monitoring and proactive management. Pharmacodynamic differences between palbociclib, ribociclib, and abemaciclib justify a personalized treatment approach based on patient characteristics and the specific tolerability of each agent, supported by an in-depth understanding of their mechanisms of action and an optimized therapeutic strategy.

Differences in efficacy and tolerability among palbociclib, ribociclib, and abemaciclib may be attributed to distinct pharmacological mechanisms, such as selectivity for CDK4 versus CDK6,

toxicity profiles, and routes of administration. These factors, along with variations in clinical trial design, may influence outcomes related to overall survival and guide the selection of the most appropriate treatment for each patient.

While chemotherapy remains the standard treatment in severe forms of visceral crisis, CDK4/6 inhibitors may represent a viable therapeutic option in selected cases. This consideration is supported by evidence demonstrating survival benefits and favorable objective response rates even in patients with visceral disease, provided that the severity of vital organ dysfunction and the individual clinical profile are carefully evaluated.

Findings from two recent studies suggest that, although CDK4/6 inhibitors confer clinical benefits in the treatment of metastatic HR+/HER2− breast cancer, their use in the first-line setting may not be cost-effective according to current economic models. Moreover, they may be associated with increased toxicity without significant improvements in overall survival, progression-free survival, or quality of life compared to second-line administration. These findings support a reassessment of therapeutic strategies and encourage future research aimed at optimizing treatment sequencing.

An updated analysis of the safety profile of CDK4/6 inhibitors, based on aggregated data from key randomized Phase II and III trials, indicates that while palbociclib, ribociclib, and abemaciclib are generally well tolerated, each agent exhibits a distinct toxicity profile that must be considered in clinical decision-making. Neutropenia is most frequently associated with palbociclib and ribociclib; QTc interval prolongation and hepatotoxicity are primarily linked to ribociclib; and pronounced gastrointestinal toxicity is characteristic of abemaciclib. These adverse effects, although frequent, can be effectively managed through vigilant monitoring and appropriate dose adjustments, emphasizing the importance of early recognition of toxicities to optimize therapeutic safety.

Over the past decade, the recognition of quality of life (QoL) as a key endpoint in oncology has marked a fundamental paradigm shift, reflecting a transition from a model focused solely on survival prolongation to one oriented toward the holistic well-being of the patient. In this context, QoL assessment using validated, multidimensional tools has become essential for understanding the subjective experience of women with breast cancer in relation to their disease and treatment. This contributes to informed clinical decision-making, the optimization of

therapeutic interventions, and the integration of the human dimension into modern oncologic practice.

Chapter 3 outlines the hypothesis and general objectives of the study.

Working hypothesis

It is already well known that the use of CDK4/6 inhibitors in the treatment of oncology patients has a significant impact on survival, clinico-biological evolution, and quality of life, and this impact is influenced by multiple variables, including the type of inhibitor used, the presence of comorbidities, the histological and metastatic characteristics of the tumor, as well as the clinical response of patients. Also, certain symptoms, such as fatigue and insomnia, may be predictors of disease progression, and differences between types of CDK4/6 inhibitors in terms of toxicity and adverse effects could influence treatment adherence and overall survival.

General objectives

1. **To evaluate the impact of treatment with CDK4/6 inhibitors on overall survival (OS) and progression-free survival (PFS)** – Investigation of the correlation between treatment duration and the clinico-biological characteristics of patients, depending on the type of CDK4/6 inhibitor used.
2. **To analyze the influence of comorbidities on the efficacy and tolerability of therapy with CDK4/6 inhibitors** – Determination of how associated conditions may influence therapeutic response, treatment duration, and quality of life in oncology patients.
3. **To identify the main symptoms that affect the quality of life in patients treated with CDK4/6 inhibitors** – With emphasis on fatigue, insomnia, pain, gastrointestinal disorders, and side effects specific to each type of inhibitor.
4. **To compare the impact of different types of CDK4/6 inhibitors on patients' quality of life** – Evaluation of differences between ribociclib, palbociclib, and abemaciclib in terms of toxicity, adverse effects, and their influence on physical, social, and emotional functioning.
5. **To determine correlations between clinico-biological characteristics and quality of life** – Investigation of how parameters such as tumor histological grade, metastatic status

at diagnosis, and lymph node status influence patients' perception of their own health status.

6. **To evaluate the role of psychological symptoms in patient evolution** – Analysis of the influence of depression, anxiety, and stress on treatment adherence and overall survival.

7. **To formulate recommendations for optimizing the care of oncology patients treated with CDK4/6 inhibitors** – Based on the obtained results, proposing therapeutic and supportive strategies to improve treatment tolerability, adherence, and quality of life in the current oncologic context.

These objectives aim not only to deepen the understanding of the impact of treatment with CDK4/6 inhibitors on oncology patients, but also to identify predictive factors that could guide therapeutic decisions and improve strategies for the management of symptoms and therapy-related toxicities.

Chapter 4 describes the general research methodology.

This study was conducted on a group of 95 female patients diagnosed with HR+/HER2− metastatic breast cancer and treated with CDK4/6 inhibitors. Of these, 76 patients met the inclusion criteria for the second study, and the results reported in the second study are derived exclusively from this carefully selected group. In the second study, which involved questionnaire-based assessment, three patients with psychiatric disorders, seven patients who had received CDK4/6 inhibitor therapy for less than three months, eight patients who refused to respond, and one male patient were excluded.

Demographic data and clinical characteristics of the patients were retrospectively extracted from electronic medical records during clinical evaluations conducted at Elias University Emergency Hospital in Bucharest, Romania, between January 2018 and January 2024. Quality of life data were prospectively collected using four questionnaires: EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients), Depression, Anxiety, and Stress Scale-21 (DASS-21), Multidimensional Fatigue Inventory (MFI), and the Pittsburgh Sleep Quality Index (PSQI).

The study protocol was approved by the Ethics Committee of Elias University Emergency Hospital, Bucharest, Romania (no. 1489/01.03.2024). The study design, data analysis, result interpretation, manuscript drafting, and revisions were carried out in accordance with the Declaration of Helsinki and the guidelines of the Committee on Publication Ethics (COPE). All collected data were anonymized, considering the observational nature of the study and excluding any information that could allow for formal patient identification.

Inclusion criteria: Female patients aged ≥18 years, previously or currently treated with CDK4/6 inhibitors, with a histopathologically confirmed diagnosis of HR+/HER2− breast cancer, and at least three visits to the oncology department.

Exclusion criteria: Male patients or female patients under 18 years of age, critically ill patients or those with mental/psychiatric disorders, patients who had received CDK4/6 inhibitor therapy for less than three months, patients who did not complete all four questionnaires, or those who refused to answer all questions.

The collected data included the following variables: age at diagnosis, place of residence, histological grade, stage at diagnosis (locally advanced vs. metastatic disease), location of metastases, type of CDK4/6 inhibitor used, duration of CDK4/6 inhibitor therapy, associated endocrine therapy, menopausal status, Ki67 percentage, CA15-3 levels at diagnosis, comorbidities, survival/death status, family history of cancer, and chemotherapy administered before or after CDK4/6 inhibitor treatment. The presence or absence of a history of COVID infection, as well as the presence or absence of thrombosis, were also assessed.

Chapter 5 describes the first study conducted as part of the doctoral thesis, with a focus on the clinico-biological profile of patients with HR+/HER2− metastatic breast cancer treated with CDK4/6 inhibitors. This is a retrospective analysis and provides prognostic correlations. Chapter 5 is divided into the following subchapters:

1. Detailed analysis of the clinico-biological characteristics of the patients included in the study
2. Analysis of the types of CDK4/6 inhibitors and their impact on survival
3. Correlation of biological characteristics with prognostic outcomes

4. Toxicity and dose modification
5. Analysis of clinico-biological characteristics associated with the type of CDK4/6 inhibitor and endocrine therapy
6. Distribution of patients according to the type of endocrine therapy used
7. Evaluation of progression-free survival (PFS), overall survival (OS), and total treatment time (TOT) by CDK4/6 inhibitor
8. Detailed interpretation of statistical data regarding PFS, OS, and TOT by CDK4/6i type
9. Analysis of the impact of CDK4/6 inhibitors according to associated endocrine therapy and patient age
10. Analysis of independent variables associated with progression-free survival (PFS), overall survival (OS), and total treatment time (TOT)

The detailed analysis of the clinico-biological and therapeutic characteristics of the patients included in the study highlights significant differences in disease evolution depending on age, metastatic status, and type of treatment administered. Ribociclib was associated with the highest survival rate. In addition, the presence of multiple metastases and a high Ki67 index were correlated with a less favorable prognosis. These findings support a personalized therapeutic approach, with particular emphasis on selecting CDK4/6 inhibitors based on the individual clinico-biological characteristics of each patient.

The only statistically significant difference between CDK4/6 inhibitor groups was histological grade at diagnosis ($p = 0.006$), with ribociclib being used exclusively in patients with grade G2. Regarding endocrine therapy, letrozole/anastrozole was more frequently associated with isolated bone metastases ($p = 0.007$). For all other variables analyzed, no significant differences were observed between groups, suggesting a relatively homogeneous distribution of patients according to the type of treatment administered.

Palbociclib was associated with a longer treatment duration and greater overall survival. Statistically significant differences were observed only for treatment duration (TOT), while for PFS and OS, no significant differences were identified between the types of CDK4/6 inhibitors.

These results suggest the need for further analyses to clarify the impact of each CDK4/6 inhibitor on survival and disease progression.

Ribociclib was more frequently used in patients under 50 years of age in combination with fulvestrant, where it showed a longer treatment duration and extended progression-free survival. In contrast, in patients over 50 years of age, the combination with letrozole/anastrozole was more favorable. Palbociclib provided the longest treatment duration and best progression-free survival in combination with fulvestrant, especially in patients under 50, but also showed solid results in older patients, particularly when combined with letrozole/anastrozole. Abemaciclib showed variable results, with the longest progression-free survival observed in patients over 50 treated with letrozole/anastrozole, but it was associated with reduced overall survival, especially in this combination.

The total duration of CDK4/6 inhibitor treatment was significantly influenced by several factors, including histological grade at diagnosis, presence of metastases, administration of radiotherapy, type of CDK4/6 inhibitor used, treatment-related toxicity, and history of COVID infection.

Regarding overall survival, this was significantly influenced by the treatment administered after CDK4/6i therapy and by the type of endocrine therapy used. In contrast, progression-free survival was not significantly influenced by most of the variables analyzed, except for a possible effect of radiotherapy.

These results suggest that careful selection of treatment, taking into account the specific clinico-biological factors of each patient, could optimize therapeutic strategies and improve oncologic prognosis.

Chapter 6 investigates the assessment of quality of life in patients with HR+/HER2− metastatic breast cancer treated with CDK4/6 inhibitors. This is a multidimensional analysis that highlights determining factors. Chapter 6 is divided into the following subchapters:

1. Analysis of quality of life in oncology patients – general data
2. Analysis of the correlation between quality of life and the type of CDK4/6 inhibitor
3. Analysis of the correlation between quality of life and the evolution of oncology patients
4. Analysis of the correlation between quality of life and comorbidities in oncology patients

5. Analysis of quality of life during the COVID pandemic
6. Perspective on quality of life in oncology patients

The analysis of the correlation between quality of life and the type of CDK4/6 inhibitor revealed that most of the evaluated parameters showed no statistically significant differences between treatment groups, indicating a generally comparable impact of the three therapies on patients' physical, emotional, and social functioning. However, insomnia and diarrhea were the only symptoms for which statistically significant differences were observed, with ribociclib being associated with a lower impact on sleep problems, while abemaciclib was more frequently correlated with diarrhea. Additionally, ribociclib was associated with better sleep quality, which may represent an important clinical advantage for patients experiencing circadian rhythm disorders in the context of oncologic treatment. In the remaining analyzed dimensions, no statistically significant differences were identified, suggesting that from the perspective of quality of life, the three treatments offer similar benefits in symptom control and the maintenance of general functioning in oncology patients.

Regarding statistically significant differences between surviving and deceased patients, two variables were identified as relevant: loss of appetite ($p = 0.036$), which was significantly higher in deceased patients, and mental fatigue ($p = 0.003$), which had a strong correlation with unfavorable prognosis. These results suggest that malnutrition and the severe psychological impact of the disease may negatively influence the survival of oncology patients.

Additionally, two variables were identified as having near-statistically significant differences: physical fatigue ($p = 0.094$) and nausea and vomiting ($p = 0.088$), both being reported at higher levels by deceased patients. These data suggest that the severity of fatigue and gastrointestinal symptoms may impact disease progression and warrant more detailed investigation in future studies.

Regarding the remaining indicators, no statistically significant differences were identified between the analyzed groups, suggesting that in terms of most quality-of-life dimensions, surviving and deceased patients had similar experiences. However, the data indicate that mental fatigue and loss of appetite are critical factors that may influence the prognosis of oncology

patients and require careful monitoring as part of palliative care and nutritional support strategies.

Regarding statistically significant differences, two variables were identified as relevant: insomnia ($p = 0.014$), which was reported at a significantly higher level by patients with comorbidities, and constipation ($p = 0.046$), which was significantly more frequent in this group. These results indicate that sleep disturbances and gastrointestinal dysfunctions may be amplified in the presence of comorbidities, requiring close monitoring and appropriate therapeutic management.

Additionally, three variables were identified as having near-statistically significant differences: fatigue ($p = 0.091$), which was reported at a higher level by patients with comorbidities; depression ($p = 0.075$), which had higher scores in this group; and stress ($p = 0.121$), which was also more frequently reported. These results suggest that patients with associated conditions may be more prone to chronic fatigue and emotional disorders, highlighting the importance of an integrated care approach that addresses both the physical and psychological aspects of the disease.

The analysis of the correlation between quality of life and comorbidities revealed that patients suffering from associated conditions have a higher risk of experiencing severe symptoms, including pronounced insomnia, frequent constipation, increased levels of fatigue, and a stronger psychological impact manifested through elevated depression and stress. These results underscore the need to develop personalized strategies for symptom and mental health management in patients with comorbidities, aiming to improve their quality of life and optimize oncologic care. Moreover, the data suggest that supportive interventions such as psychological counseling and nutritional monitoring may play an essential role in reducing the negative impact of comorbidities on the progression of oncology patients.

The evaluation of quality of life in oncology patients undergoing treatment with CDK4/6 inhibitors revealed significant impairments in physical, social, and emotional functioning, with considerable variability among patients. Fatigue proved to be a central symptom, having a major impact on patients' ability to function and their motivation, highlighting the importance of continuous monitoring of this symptom. Sleep-related problems were frequently reported and correlated with other symptoms, including fatigue and stress. Financial difficulties and nausea

were less common compared to other issues, although some cases indicated increased severity. Stress and depression levels ranged from moderate to high, with significant variability between patients, suggesting the need for a personalized approach to improving their quality of life.

The detailed analysis of quality of life among oncology patients reveals that although the general perception of health status is moderate to good, the impact of treatment and disease on physical and social functioning is significant. Fatigue and insomnia are the main symptoms affecting patients, having a major negative effect on daily activities and emotional well-being. Although pain and loss of appetite are reported by patients, they do not constitute dominant symptoms in the overall quality of life. Cognitive functioning is largely preserved, but difficulties in the social sphere indicate a possible need for additional interventions to reduce isolation and improve social support.

These data highlight the importance of an integrated approach to the care of oncology patients, aimed not only at managing physical symptoms but also at optimizing psychological and social health in order to improve long-term quality of life.

Conclusions of the studies

The detailed analysis of the impact of CDK4/6 inhibitors on quality of life and the clinico-biological characteristics of oncology patients highlighted a series of critical factors influencing prognosis and overall well-being. The study demonstrated that although the overall perception of health status is moderate to good, there are significant variations across the different dimensions of quality of life, with notable effects on the physical, social, and psychological functioning of patients. Furthermore, biological factors such as the histological grade of the tumor, metastatic status at diagnosis, and the type of treatment administered significantly influenced survival and therapeutic response.

Patients with grade G2 histological tumors had the longest average duration of CDK4/6 inhibitor treatment, indicating better tolerance and a potentially more favorable therapeutic response compared to those with G1 or G3 tumors. Moreover, patients with metastatic status at diagnosis had a significantly longer treatment duration, suggesting that CDK4/6 therapy was effective in delaying disease progression in this group. In contrast, factors such as nodal status at diagnosis and Ki67 percentage did not show significant differences regarding overall survival or treatment duration.

Fatigue proved to be the main reported symptom, having a major impact on daily activities and quality of life, with higher values among patients with comorbidities and those with unfavorable disease progression. Insomnia was identified as a recurrent symptom, significantly more frequent among patients with comorbidities, suggesting a correlation between associated conditions and sleep disorders. Constipation was significantly more common in patients with comorbidities, indicating the need for careful management of treatment-induced adverse effects.

Physical functioning was significantly more affected in patients with comorbidities, who reported major limitations in carrying out daily activities. Social functioning was also considerably reduced, with a tendency toward social isolation and difficulties in maintaining interpersonal relationships, underlining the importance of social support in the management of oncology patients. From an emotional perspective, patients with comorbidities presented higher levels of stress and depression, indicating the need for personalized psychological interventions for this patient category.

Patients who reported higher levels of mental fatigue and loss of appetite had unfavorable outcomes, with these symptoms being significantly correlated with a poorer prognosis. Additionally, nausea and vomiting were more frequent in patients with a reserved prognosis, suggesting that these symptoms may represent important markers of disease progression. Moreover, patients who continued with post-CDK4/6i treatments—especially chemotherapy—achieved longer overall survival, indicating a possible benefit of sequential therapies.

Ribociclib was associated with better sleep quality and a lower incidence of insomnia compared to palbociclib and abemaciclib. On the other hand, abemaciclib was more frequently correlated with diarrhea, indicating a more pronounced gastrointestinal toxicity profile. Palbociclib had the longest treatment duration and was more often used in patients with favorable disease evolution. Additionally, ribociclib proved more effective in younger patients, while palbociclib was more frequently associated with older patients.

Patients with comorbidities reported lower quality of life, with significant negative impact on fatigue, insomnia, and constipation. They also had higher scores for depression and stress. Comorbidities were also associated with shorter treatment duration in these patients.

These findings highlight the need for a multidisciplinary approach in the care of oncology patients, including both optimal symptom management and psychological and nutritional support to improve their quality of life, alongside careful selection of therapeutic options based on the tumor's biological characteristics.

Personal Contributions

1. Identification of independent clinico-biological factors influencing the response to CDK4/6 inhibitors, highlighting the impact of histological grade, metastatic status, comorbidities, post-CDK4/6 inhibitor treatment, radiotherapy administration, type of CDK4/6 inhibitor used, as well as toxicity, on treatment efficacy. This contribution was developed in Chapter 5.2.10., paragraphs 2, 3, 4, 5, 6, and 7.
2. Comprehensive comparison of the three CDK4/6 inhibitors, emphasizing significant differences in terms of OS, PFS, and TOT. This contribution was developed in Chapter 5.2.8., paragraphs 1 and 2.
3. Three-dimensional analysis of quality of life in relation to the type of CDK4/6 inhibitor, patient outcomes, and associated comorbidities. This contribution was developed in Chapters 6.2.2., 6.2.3., and 6.2.4.
4. Analysis of the impact of symptoms on overall survival and quality of life, highlighting the role of fatigue, insomnia, and depression in treatment adherence. This contribution was developed in Chapter 6.2.1., paragraphs 4 and 7; Chapter 6.2.2., paragraph 6; Chapter 6.2.3., paragraph 4; Chapter 6.2.4., paragraphs 3 and 6; and Chapter 6.2.6., paragraph 4.
5. Development of specific recommendations for optimizing the care of oncology patients, including strategies to increase adherence and improve psychological support. This contribution was developed in Chapter 7.7., paragraph 2.

This is the first study in Romania and in Europe to evaluate quality of life in a real-world setting for patients with metastatic breast cancer treated with CDK4/6 inhibitors, using four different assessment tools.

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2. **Stanciu, I.-M**.; Pirlog, C.F.; Anghel, A.-W.; Parosanu, A.I.; Olaru, C.M.; Orlov-Slavu, C.; Iaciu, I.C.; Popa, A.M.; Vrabie, R.C.; Nitipir, C. Does the Rechallenge with Another CDK 4/6 Inhibitor in Breast Cancer Work? A Case Report and Literature Review. Medicina 2023, 59, 696. https://doi.org/10.3390/medicina59040696

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