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IMPLEMENTING ALPELISIB WITH FULVESTRANT IN METASTATIC BREAST CANCER TREATMENT: SAFETY PROFILE, FINDINGS FROM REAL-WORLD CLINICAL DATA

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Summary

Breast cancer is the most common cancer diagnosed among women in 2021in Croatia, according to the last published data by the Croatian National Cancer Registry**.** For hormonally dependent – HER2 negative metastatic breast cancer (HR+HER2– mBC) patients with PIK3CA mutations, a PIK3CA inhibitor alpelisib,combined with fulvestrant has demonstrated efficacy following prior treatment with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, as shown in clinical trials such as SOLAR-1 and BYLieve. In this analysis we discuss alpelisib implementation in real-world practice, emphasizing similarities with the clinical trials and available data for several real-world trials. In a cohort of 20 women with HR+/HER2– mBC, patient demographics, treatment duration, adverse events (AEs), and reasons for treatment discontinuation were analyzed.

Seventy percent of patients experienced treatment-related adverse events (AEs), most frequently hyperglycemia, rash, and oral mucositis, over the median three-month course of alpelisib.

In 65% of cases, adverse events (AEs) required dosage modifications or interruptions, and 40% of patients discontinued their treatment. Our real-world findings show a higher frequency of AEs and less favorable treatment tolerance, compared to clinical trial data. These findings are consistent with prior real-world studies but differ from the more rigorous compliance and monitoring in clinical trials. Our results highlight the importance of improved safety procedures and monitoring to improve treatment compliance in real-world settings. It highlights awareness of how challenging it is to manage therapy-related toxicity in standard clinical practice, which can affect treatment sustainability.

KEYWORDS: *alpelisib, breast cancer, metastatic disease, safety*

INTRODUCTION

Breast cancer is the most common cancer diagnosed among women in 2021. in Croatia, according to the last published data by the Croatian National Cancer Registry**.** The incidence rate was 145,60/ 100,000 women(1). According to the SEER database, the most common subtype is hormone-receptor (HR) positive human epidermal growth factor receptor (HER2) negative, with 88.1 new cases per 100,000 women between 2017 and 2021(2). Inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) have changed the landscape of HR-positive, HER2-negative advanced breast cancer, from sequential endocrine monotherapy to

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combination therapy in first-line treatment. The results from pivotal trials of abemaciclib, palbociclib, and ribociclib have demonstrated consistent efficacy in improving progression-free survival (PFS) as first-line therapies(3). The most commonly used CDK4/6 inhibitors have a low absolute risk of significant adverse events (AEs) and treatment discontinuation rates, based on meta-analysis by Costa et al(4). For patients with HR+ metastatic breast cancer, disease progression is always a challenge, even with the availability of effective endocrine therapies (ETs). Mutations in the phosphatidylinositol 3-kinase (PI3K) gene, which encodes the isoform of the PI3K gene, are recognized as negative prognostic factors(5). This mutation is found in nearly 40% of patients with HR-positive, and HER2-negative breast cancer, and contributes to resistance to endocrine therapy(6). Alpelisib is approved for the treatment of patients with metastatic HR-positive breast cancer with PIK3CA mutation, who have received prior endocrine therapy, based on results from SOLAR-1, a phase III trial(7,8). Since CDK4/6 inhibitors in combination with endocrine therapy are the standard of first-line treatment of HR-positive advanced BC, it was crucial to determine whether this population would benefit from alpelisib. To answer this question, BYLieve, a phase 2 open-label, non-comparative clinical trial was performed. BYLieve confirmed efficacy and safety of alpelisib combined with fulvestrant in patients with confirmed PIK-3CA-mutated disease, who received a CDK4/6i with endocrine therapy(9). Appropriate adverse event (AE) detection and management are informed by a thorough understanding of alpelisib's safety profile. According to the reported safety profile of alpelisib plus fulvestrant in SOLAR-1, the most frequent grade 3/4 adverse events (AEs) include rash, diarrhea, and hyperglycemia(7,10). In the SOLAR-1 trial 25% of patients, and 14% of patients in the BYLieve trial, discontinued treatment with alpelisib due to AEs(7,9).

This paper discusses alpelisib's implementation in real-world practice, emphasizing similarities with the BYLieve and SOLAR-1 trials, as well as available data for several real-world trials.

MATERIALS AND METHODS

This single-institution study included patients treated at the Division of Medical Oncology at the University Hospital for Tumors, of Sestre milosrdnice University Hospital Center, in Zagreb. We retrospectively analyzed electronic records of patients with HR-positive HER2 negative, PIK-3CA-mutated metastatic breast cancer, who were treated with alpelisib in combination with fulvestrant, from March 2021 to August 2024. All individuals who received alpelisib treatment and discontinued it, together with the documented cause for discontinuation, were identified by a thorough evaluation of their medical records. Aleplisib's duration and maximum tolerable dosage were also noted. As part of their routine clinical care, patients were followed up, and chart reviews were used to obtain follow-up data. Patients could have had no more than two previous anticancer therapies and no more than one previous chemotherapy regimen in the advanced setting. They also had to have a fasting plasma glucose level of no more than 7·7 mmol/L and glycated hemoglobin A1c (HbA1c) of no more than 6.4%, including patients with well-controlled type 2 diabetes. On day 1 of each 28-day cycle and day 15 of cycle 1, patients were given 500 mg of fulvestrant intramuscularly and 300 mg of alpelisib orally once daily. Treatment persisted until progression of disease, the unacceptable toxicity, death, or the treatment was discontinued for any other reason. A maximum of two dose reductions of alpelisib (dose level –1 250 mg/day; dose level –2 200 mg/day) were permitted for patients who were unable to tolerate the medication because of adverse effects.

RESULTS

Alpelisib was administered to 20 HR-positive HER2-negative metastatic breast cancer women with PIK3CA mutations, out of the 25 female patients who were qualified for this study. For various reasons, treatment never began in five of them. All enrolled patients were female, and median follow up was 3,5 months. Patient characteristics at baseline for the full analysis set are shown in Table 1.

In all patients, the endocrine partner was fulvestrant. Treatment is ongoing in three patients, median number of the alpelisib cycle is 3.5, ranging from 1 to 15. Among 17 patients who discontinued treatment with alpelisib, the median duration of alpelisib treatment is three months (range 0-7 months). All patients had measured fasting glu-

Table 1.

Baseline clinical/demographic characteristics.

Median age (years)	66 (45 – 82)	
Menopausal status	Premenopausal 1	
	Postmenopausal 19	
Comorbidities	Yes	14
	No	6
	Diabetes type 2	4
	Prediabetes	1
Neo/adjuvant treatment	8 (40%)	
Adjuvant treatment	12 (60%)	
Treatment before alpelisib[1]	Palbociclib	12
	Ribociclib	9
	Aromatase inhibitors	9
	Fulvestrant	11
Median duration on CDK4/6i months (range)	25,5 (8-49)	

Table 2.

Toxicity profile.

Adverse event n (%)	Hyperglicemia	9 (64%)
	Rash	4 (29%)
	Mucositis	3 (21%)
Dose reductions n (%)	1st	5 (25%)
	2nd	6 (30%)
Time to dose reduction in weeks; median (range)	1st	2 (2-24)
	2nd	12 (4-16)
Treatment discontinuation n (%)	8 (40%)	

cose levels at the beginning of treatment with alpelisib, while HbA1c was missing in seven. Regulated diabetes type 2 was present in four patients, and one patient had prediabetes. Adverse events of any grade were reported for 14 (70%) of 20 patients; all had at least one adverse event considered to be treatment-related. The most frequent adverse events were hyperglycemia (nine [64%]), rash (four [29%]), and oral mucositis (three [21%]). Some of the patients experienced more than one adverse event. Of patients who were diabetic at baseline, four (75%) had hyperglycemia adverse events. Among all included patients, 65% had adverse events requiring dose interruptions or adjustments. Toxicity profile is summarized in Table 2. Adverse events leading to treatment discontinuation occurred in 40% of patients. Chemotherapy was most commonly used subsequent therapy after progression on alpelisib and fulvestrant treatment.

DISCUSSION

A real-world experience with alpelisib at our institution is presented in this paper, along with the most frequent adverse events, causes of drug dose reductions or interruptions, and reasons for discontinuation of alpelisib treatment. Adverse events were consistent with the reported safety profile of alpelisib. With 70% of patients reporting at least one AE considered to be treatment-related, we report a notable rate of alpelisib-induced adverse events. The prevalence of adverse events in our study is significantly higher than that found in the SOLAR1 and BYLieve trials, but this is in concordance with one trial from real-world data by Alaklabi et al(11). In our study, the most common AE were hyperglycemia (64%), rash (29%), and oral mucositis (21%), what is similar to other two real-world data trials by Miller at al. and Alaklabi et al. (hyperglycemia– 66.7% and 59.3%, rash– 45.5% and 22.2%, respectively) (11,12). It is evident from the data that the vast majority of patients on alpelisib develop hyperglycemia as a serious adverse event. Dose interruptions/ modifications due to adverse events were required in 65% of patients which is similar to available real-world data. In a trial by Alkalabi et al., dose interruptions/reductions were required in 51.9% of patients, while in a trial by. Cheung et al. it happened in 48% of patients(11,13). Overall, fewer treatment discontinuations due to adverse events were observed in BYLieve (21%) than in SOLAR-1 (25%), which is notably lower than in our trial, where our results are concordant with available real-world data. The median duration of exposure to alpelisib was also shorter than that reported by clinical trials (3 vs 5.1–5.5 months)(7,9). Once more, the data is comparable to the real-world trials mentioned(11,13). The differences in study design (prospective versus retrospective), sample size, and patient selection/populations could be one reason for the dissimilarities in results. Furthermore, our study is more representative of how AEs are tracked and managed in the real world setting, as compared to the clinical trials, which had rigor-

1 Due to the toxicity of one CDK4/6 inhibitor, one patient received treatment with both palbociclib and ribociclib.

ous adherence to AE procedures. For instance, 35% of individuals in our study had no documented HbA1c at the beginning of treatment. Furthermore, the high probability of permanent alpelisib discontinuation in our cohort may indicate that treating oncologists are unable to quickly control adverse events (even at lower alpelisib dosages), as alpelisib can frequently be safely sustained, provided the AE is treated and well monitored. This emphasizes the importance of precise specialist's (in this case endocrinologist's) involvement.

CONCLUSION

Overall, our trial's safety profile indicates that additional safety measures are needed to successfully control and monitor adverse events and to improve tolerance. Alpelisib and fulvestrant therapy optimization can be supported by ongoing education and the implementation of management measures. However, our findings are consistent with other comparable real-world trials, implying that the adverse events of this combination are predictable and manageable. In conclusion, when deciding on a course of treatment for our patients, it is crucial to use and take into account the constantly growing real-world evidence regarding the toxicity and efficacy of alpelisib, in addition to data from clinical trials.

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Sažetak

PRIMJENA ALPELISIBA U KOMBINACIJI S FULVESTRANOM U LIJEČENJU PROŠIRENOG RAKA DOJKE: TOKSIČNI PROFIL, ISKUSTVO IZ STVARNE KLINIČKE PRAKSE

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Karcinom dojke je najčešće dijagnosticirani karcinom u žena u 2021. godini prema posljednje dostupnim podatcima Registra za rak pri Hrvatskom zavodu za javno zdravstvo. Studije SOLAR-1 i BYLive su pokazale učinkovitost alpelisiba, PIK3CA inhibitora u kombinaciji sa fulvestrantom u liječenju hormonski ovisnog, HER2 negativnog matastatskog raka dojke (HR+HER2-mBC), a nakon progresije na liječenje sa inhibitorima ciklin ovisnih kinaza 4/6. U našem istraživanju smo prikazali primjenu alpelisiba u našoj svakodnevnoj kliničkoj praksi, usporedili smo s kliničkim studijama jednako kao i s nekoliko studija iz stvarnog života. U kohorti od 20 žena s HR+/HER2-mBC, analizirani su demografski podaci pacijentica, trajanje liječenja, neželjene nuspojave (AE) i razlozi za prekid liječenja. Sedamdeset posto pacijenata doživjelo je nuspojave povezane s liječenjem (AE), najčešće hiperglikemiju, osip i oralni mukozitis. U 65% slučajeva nuspojave (AE) zahtijevale su prilagodbu doze ili pauze u liječenju, a 40% pacijenata prekinulo je liječenje. Naši rezultati iz stvarne kliničke prakse pokazuju veću učestalost nuspojava u usporedbi s podacima kliničkih ispitivanja. Naši rezultati su u skladu s drugim studijama iz stvarne kliničke prakse, ali se razlikuju od rigoroznijeg praćenja koje je bilo u kliničkim ispitivanjima. Naši rezultati naglašavaju važnost pomnog praćenja bolesnika u svrhu poboljšanja suradljivosti tijekom liječenja alpelisibom. Također, naglasak je na tome koliko je izazovno upravljati toksičnošću povezanom s terapijom u svakodnevnoj kliničkoj praksi, što može utjecati na kontinuitet i ishode liječenja.

KLJUČNE RIJEČI: *alpelisib, rak dojke, metastatska bolest, sigurnost*