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EFFICACY OF CDK4/6 INHIBITOR IN TREATMENT OF METASTATIC BREAST CANCER AND COLON CANCER

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ABSTRACT
Background: Efficacy of CDK4/6 inhibitors in treatment of metastatic breast cancer and colon cancer. **Case report:** A 52-y.o. woman was diagnosed with an invasive left-sided ductal breast cancer, G3 - T2N0M0; ER (3+), PR (+), HER2 (-), Ki67-11%. She underwent a radical mastectomy, followed by adjuvant chemotherapy and hormone treatment with Tamoxifen. A year later she was diagnosed with a colorectal cancer-low grade, G1; adenocarcinoma - T3N1M1 with liver metastases. After a biopsy, which revealed that the metastases are coming from the breast (ER+/HER 2(-) Breast cancer - (GATA (3+)), she was restaged as T3N1M0. The patient started treatment with Ribociclib 600mg/d + Letrozole 2,5mg/d with a complete response of the disease after three months of treatment. Due to G3 neutropenia, the dose was adjusted to 400 mg/d. Last restaging: July 2019 – stable disease and a good quality of life. This case approves that the CDK 4/6 inhibitors are able to manage visceral metastases and to provide long-term survival without worsening the quality of life. **Conclusion:** Her disease is successfully managed with CDK4/6 inhibitor together with hormonal therapy, which proves the effect of the CDK 4/6 inhibitors in treatment not only to breast cancer. Six months after there are no signs of relapse of the colon cancer. Despite the stage of the second cancer – T3N1M0, the patient did not undergo adjuvant treatment for the colon cancer.

KEYWORDS: Metastatic breast cancer; colon cancer; hormone therapy; efficacy; safety profile.

INTRODUCTION
Breast cancer is the most common malignant disease among women – over 2,1 million women are affected annually according to WHO.[1] It is also the most frequent reason for death among women who had suffered once in a lifetime with an oncological disease. Breast cancer is a multifactor heterogeneous disease with epidemiologic significance for the society around the world. It affects most frequently the postmenopausal patients at the age 50-70y. old. However, around 25% of the cases are below the age of 50 and 5% are even under 35 y. old.[2]

The standard treatment of breast cancer is complexed. It includes surgical methods, chemo- and radiotherapy, endocrine therapy for hormonal sensitive tumors and targeted therapy for HER2-expressing tumors. Breast carcinomas can be classified in different subgroups depending on their histology. This is crucial in the clinical practice in order to create the convenient therapeutic strategy. Main subgroups are: Luminal A (HR+/HER2-); Luminal B-like (HR+/HER2-) high Ki67; Luminal B-like (HR+/HER2+) any Ki67; Non-Luminal (HR-/HER2 overexpression); Basal-like – TNBC (HR-/HER2-); typical basal-like / unclassified.[2]

Hormonal positive (Luminal A; Luminal B) are around 70% of the newly diagnosed tumors. Most of them show good results in treatment with endocrine agents. Despite this fact, 40% of the patients are getting resistant to this treatment, which requires creating new molecules to prevent and to fight over this resistance. In the last couple of years successfully started the combined therapy with CDK4/6 inhibitors together with endocrine therapy in hormonal sensitive metastatic breast cancer. To the group of the CDK4/6 inhibitors belong Abemaciclib (Verzenio®), Palbociclib (Ibrance®) and Ribociclib (Kisqali®).

CASE REPORT
This report presents the case of a 52 years old postmenopausal Caucasian woman, who was diagnosed in February 2017 with an invasive ductal carcinoma. – G3 on the left breast. A radical mastectomy a modo Auchincloss was performed and the staging is as follows – T2N0M0, immunohistochemistry (IHC): ER (3+); PR (+); HER2(-); Ki67 = 11%; E-cadherin-reduced expression. After the mastectomy the patient had adjuvant chemotherapy – 6 cycles EC (April-August, 2017). The woman started adjuvant hormonal treatment with Tamoxifen. EndoPredict® Report provided

information for high risk of relapse of the disease: EPclin Score-3.5, EPclin 10y risk-11%, EPclin Class-high risk**.** In June 2018 a computerized axial tomography (CAT) scan was performed, which did not show any evidence neither for metastatic lesions nor for relapse.

The patient has a negative family history. In the past history, at the age of 50 the patient underwent a total hysterectomy with bilateral salpingoovariectomy due to myoma of the uterus. As co-morbidity the patient has a left-sided thoracic wall Basal-Cell Carcinoma (BCC), which was reevaluated and verified as BCC after excision of the skin lesion in October 2018.

In September 2018 the patient was diagnosed with a colorectal cancer (CRC), which was confirmed as low-grade adenocarcinoma of the colon sygmae. She underwent a laparoscopic resection of the sigma with termino-terminal sigmo-recto anastomosis and resection of the liver metastasis – TNM staging is as follows: T3N1M1 with liver metastases and infiltration of the tumor in the pericolic adipose tissue; metastases were found in 2 out of 13 lymph nodes. The histology of the liver metastases revealed that it is dissemination from the previously treated breast carcinoma – IHC: ER(+)/HER2(-), non-differentiated breast carcinoma. The colon cancer was restaged as T3N1M0. A CAT scan was performed in October 2018: Multiple hypodense liver lesions of various sizes (the biggest - in 6th segment, 1.44/1.28 cm axial size). In November was performed a full-body skeletal scintigraphy: no SPECT/CT evidence for metabolically active bone metastases.

Since then, the patient had started therapy with Ribociclib 600mg/d + Letrozole 2,5mg/d for the first two cycles. Later, due to a Grade III neutropenia the dose of Ribociclib was adjusted to 400mg/d. In February 2019 an abdominal contrast enhanced ultrasonography (CEUS) states: "the findings correspond to simple liver cysts and responding to the ongoing therapy (regressing) former methastases". A colonoscopy in March 2019 found a polypus of the sigma and internal hemorrhoids. In May 2019 a CAT scan was performed, which showed reduction in the size of the liver metastases – 0.81/0.76cm compared to previously 1.44/1.28cm. Also, there is no evidence for newly occurred lesions in the liver. Partial response. The patient benefits from this type of treatment, as she is not exposed to additional effects of chemotherapy. Moreover, she has stable disease regarding the colon cancer and good response from the liver lesions. The treatment is still ongoing and the quality of life is not changed.

DISCUSSION

More recent data has been published about the combination of antiestrogenes with other targeted agents in the first and later lines in the treatment of HR+ metastatic breast cancer. CDK4/6 inhibitor Palbociclib and Letrozole have demonstrated a PFS advantage for treatment of metastatic disease. In the PALOMA-2 phase III trial the addition of Palbociclib to Letrozole treatment resulted in a 10-month improvement in PFS compared to Letrozole alone (24,8 vs. 14,5 months; p=0,0004) in postmenopausal women with previously untreated metastatic disease with an HR for disease progression or death of 0,58 (95%; 0,46-0,72; p<0,001) No OS benefit has been reported.[3]

Lately there are lots of studies in-vitro and in-vivo (using xenografts) on the effects of CDK4/6 inhibitors to other malignancies, namely because of the safety profile and the large expression of cyclin-depending kinases in the tumors. These agents are involved in numerous studies for treatment of other types of cancer – more often colorectal or NSCLC and even for melanoma.

In February 2019 a study of C L Lee, S Toomey, A Farrelly, B Hennessy[4] was examining the combined effect of CDK4/6 inhibitor together with PI3K-inhibtors. The study found that the combination between Palbociclib + Gedatolisib has clear synergistic antiproliferative effect in CRC cell lines with common mutations arising from MAPK & P13K pathways. These mutations might play crucial role in the future when the treatment against colorectal cancer simply does not show any effect.

In another study Abemaciclib was found to have positive effects in patients dealing with gynaecological malignancies, but also brain glioblastomas, non-small cell lung cancer, melanoma and colorectal carcinoma. This study showed that 3 out of the enrolled 17 patients glioblastoma (n=17) have benefited from Abemaciclib[5], same with one patient with EGFR and another with TP53-mutation in the NSCLC-group (n=68); in the melanoma group one patient achieved RECIST partial response and 6 patients achieved stable disease (n=26), these patients with metastatic melanoma expressed molecular alterations (NRAS mutation and copy-number loss at the INK4 locus), which have induced aberrant kinase activity of CDK4 and CDK6. In the colorectal cancer cohort (n=15) 2 patients have achieved stable disease as one of them with a tumor that harbored both KRAS and TP53 mutations.

Combination of CDK4/6 inhibitor and MEK-inhibitor is not studied only for breast cancer treatment.[6] A study published in 2016 reveals that Palbociclib together with Trametinib is a well tolerated treatment combination for colorectal cancer in xenograft models for both KRAS/BRAF wild-type and even BRAF mutation(+). In 2017 another study proves the correlation between KRAS-mutation and co-targeting of CDK4/6 and MEK inhibitors. The study was done in cell line models with KRAS m(+), BRAF m(+) and normal colon cancer cell lines. In this study was found out that Palbociclib together with a MEK-inhibitor (PD0325901) has a beneficial effect in both KRAS m(+) and BRAF m(+), but not in normal epithelial cells. This was proven through observation both in vitro and in vivo with

downregulation of the KRAS-associated gene signature.[7]

CONCLUSION

CDK4/6 inhibitors combined with hormonal agents successfully treat HR(+)/HER2(-) metastatic breast cancer. Their safety profile and the prolonged PFS, that they assure is making this combination preferable compared to the chemotherapy or treating with hormonal agents alone.

Yet there are no clinical trials proving benefits in treating colorectal cancer patients with CDK4/6 inhibitor only or combined with a MEK-inhibitor or PI3K-inhibitor. Despite this fact there are promising results from study trials on xenograft models, which may lead to further trials involving cancer patients with the certain genetic mutational status.

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