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Mini Review

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT) - Current State of knowledge

Adam Szostak[1], Joanna Jonska-Gmyrek[2*]

[1]Department of Hematology, National Medical Institute of the Ministry of Internal Affairs and Administration, Warsaw, Poland

[2]Faculty of Medical and Health Sciences, Kazimierz Pulaski University of Radom, Radom, Poland

***Corresponding Author:** Joanna Jonska-Gmyrek, Faculty of Medical and Health Sciences, Kazimierz Pulaski University of Radom, Radom, Poland

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Abstract

Small Cell Carcinoma of the Ovary, Hypercalcemic Type - SCCOHT is a rare and extremely malignant gynecological tumor. Both diagnosis and treatment are currently a complex problem in clinical practice, and the prognosis of patients, despite their young age at diagnosis, remains consistently unfavorable. The aim of the study is to present current knowledge about SCCOHT, as well as the results of preclinical studies constituting potentially new therapeutic strategies, based on available literature in the Pub Med database. Promising results have been achieved by research on epigenetic therapies, CDK4/CDK6 inhibitors, immunotherapy, tyrosine kinase inhibitors, as well as the elimination of arginine from the tumor environment. However, individual case reports and the results of preclinical studies available in the PubMed database indicate that in order to improve the long-term results of SCCOHT treatment, combination therapies have to be considered.

Keywords: Small Cell Carcinoma of the hypercalcemic type; Ovarian cancer; SCCOHT; Checkpoint inhibitors; Immunohistochemistry

Introduction

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT), is a rare and highly malignant cancer of the reproductive organs. It was first presented as a separate disease entity in 1982 [1]. The 2020 WHO classification of cancers places SCCOHT in the category of „miscellaneous ovarian tumors" [2]. Occurring mainly in women under the age of 40 (median incidence approximately 24 years), accounting for less than 0.01% of all ovarian cancers. Documented cases concern patients aged 7 months to 56 years of age [3]. At the same time, it should be noted that the disease occurs much earlier in carriers of the pathogenic variant of the SMARCA4 gene [4]. Despite multidisciplinary treatment, the vast majority of patients die within 2 years of diagnosis. The 5-year overall survival rate is approximately 16%, with 33% for stage 1 disease according to the FIGO classification. What is to be said here is that the most important prognostic factor is the stage at the time of diagnosis. On top of this, the favorable prognostic factors include – age over 30 years, tumor size below 10 cm, normocalcemia, and the lack of large cells in the histopathological preparation. Statistically speaking, more than half of the patients are present with an advanced form of the disease at the time of diagnosis. It develops mainly unilaterally, rarely bilaterally, especially in a hereditary form, and in approximately 60% of cases, hypercalcemia coexists, the mechanism of which is not entirely clear. In addition to this, increasing Ca125 levels were observed in some patients. At the same time, there was no correlation between the size of the tumor and the level of Ca125 or the concentration of calcium in the blood serum [5].

Materials and Methods

The aim of the study was to systematize the current knowledge regarding SCCOHT, based on available articles,

review works, reports, and case reports. The literature available in the PubMed database was analyzed, with particular emphasis on potentially new therapeutic strategies.

Histopathology

Primary diagnosis of the disease can be very difficult. Most often, SCCOHT presents an image of densely located small, homogeneous, hyperchromatic cells with scant cytoplasm and high mitotic activity with focally occurring vesicular structures containing acidophilic, less often basophilic fluid. Their origin still remains unclear. The cell nucleus contains closely packed chromatin and a single nucleolus. Furthermore, there are small foci of mucous glands, cysts lined with mature epithelium, signet ring cells or atypical mucous cells in approximately 12% of cases. On top of this, almost 50% of the specimens show large cells with an eccentrically located nucleus and glassy acidophilic cytoplasm. SCCOHT cells show diffuse nuclear staining with antibodies against the N-terminal fragment of WT1 and focal staining with antibodies against pancytokeratin (AE1/AE3), EMA, CD10, calretinin, p53. Staining with antibodies directed against desmin, S100, inhibin, TTF-1 and steroid receptors (ER, PR) remains negative. SCCOHT cells present primarily (>95% of the examined cells) a diploid karyotype with a shortened chromosome 20. The greatest diagnostic difficulty is the differentiation of SCCOHT from juvenile granulosa cell tumor [5, 6, 7, 8, 9,10].

Pathogenesis

In the light of current knowledge, SCCOHT is a monogenic disease caused by a somatic or germline mutation in the SMARCA4 gene, responsible for the expression of the BRG1 protein. The discovery of the causative role of SMARCA4 gene mutations in the context of the pathogenesis of SCCOHT, and at the same time the use of antibodies against SMARCA4 (BRG1) in immunohistochemistry, significantly facilitated the diagnosis [11]. The BRG1 protein, which determines the acquisition of energy from ATP hydrolysis, is a subunit of the SWI/SNF chromatin remodeling complex, the intact function of which is associated with the early stages of cell line differentiation, transcription control, repair, and DNA replication [3,9,12]. The presence of SMARCA4 mutations in over 95% of SCCOHT cases justifies viewing it as a potential therapeutic as well as diagnostic target with exceptionally high sensitivity and specificity. SCCOHT cells also do not show the presence of another SWI/SNF subunit, the SMARCA2 protein, the suppression of which is a consequence of epigenetic gene silencing. In most known cancers with a defective SMARCA4 gene, the correct function of the SMARCA2 protein determines cell survival, so the above phenomenon is a kind of distinction [13,14].

Prevention

Germinal (inherited in an autosomal dominant manner) and somatic mutations of the SMARCA4 gene are primarily nonsense or frameshift mutations. The occurrence of mutations within the entire gene, without predilection for specific domains, explains the lack of pathogenic significance of mutations in exons, non-transcribed areas. Moreover, the penetrance of pathological variants of the SMARCA4 gene remains undetermined, and their germline forms are often transmitted in the paternal line. Daughters of male SMARCA4 gene mutation carriers have a 50% risk of inheriting a pathogenic variant of the gene. Currently, it is recommended to diagnose the presence of germline SMARCA4 mutation in every case of SCCOHT, the occurrence of which, based on previous observations, is estimated at approximately 43% [15]. Additionally, when tainting into account the early onset and aggressive course of the disease and the uncertain penetrance of pathogenic mutations of the SMARCA4 gene, as well as the risk of false positive screening, prevention procedures remain significantly limited. Preventive bilateral adnexectomy (RRBSO) for all carriers of SMARCA4 gene mutations (including those potentially not causing SCCOHT) has no proven benefit. RRBSO is therefore recommended for a selected group of patients, primarily from families with a positive history of SCCOHT. The appropriate age range for carrying out the above procedure has not yet been determined. The decision on RRBSO should consider the risks associated with the procedure, the consequences of iatrogenic menopause, the possibility of using hormone replacement therapy, as well as the patient's reproductive plans with the available oocyte cryopreservation procedure [16]. Early detection methods using imaging tests have no proven effectiveness [8].

Treatment – current clinical practice

It should be emphasized that due to the rarity of SCCOHT in the general population and the lack of prospective clinical trials, knowledge about cancer cell biology as well as the optimal diagnostic and therapeutic course comes from experiments on cell lines and the results of treatment of narrow groups of patients [7,17]. Currently, there are no defined guidelines available for the treatment and supervision of patients with SCCOHT [18]. Most patients are treated in accordance with the guidelines for ovarian cancer, but adjuvant therapy has not been fully defined and is most often based on regimens for the treatment of rare forms of ovarian cancer [19]. Regardless of limited data on the effectiveness of individual forms of treatment, primary cytoreductive surgery with the intention of complete resection without leaving any residual disease is the basis of therapeutic treatment. In the case of a preoperative diagnosis of SCCOHT, it is recommended (even when the macroscopic advancement of the disease corresponds to the FIGO I stage) to perform a total hysterectomy, bilateral removal of the ovaries and fallopian tubes, intraperitoneal staging, and total para-aortic and pelvic lymphadenectomy [20]. Fertility-sparing surgery may be considered in the group of patients at FIGO IA stage with excluded germline SMARCA4 mutation [21,22,23].

Adjuvant chemotherapy based on cisplatin and etoposide including BEP (bleomycin, etoposide, cisplatin), VPCBAE (vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, etoposide), PAVEP (cisplatin, doxorubicin, etoposide, cyclophosphamide) regimens is recommended for all stages of the disease [19]. If primary cytoreductive surgery is not possible (FIGO IV, unresectable lesions), treatment should begin with chemotherapy and interval cytoreductive surgery has to be considered. It has been shown that in the case of complete response to primary chemotherapy (regardless of surgical treatment), subsequent high-dose chemotherapy with stem cell transplantation improves the prognosis [24]. Radiotherapy should be considered in individual cases [25]. In the light of the latest literature, attention is drawn to the need to test the presence of checkpoint inhibitors in terms of the possibility of using effective therapy [26,27]. The authors draw attention to the need for immunohistological testing for PD-L 1. What is important to be said here is that, there is a case of a dramatic response to treatment which is seen in a 21-year-old patient treated with pembrolizumab [19]. Despite the initial chemosensitivity of SCCOHT, disease recurrence most often occurs after a short time, and the effectiveness of subsequent lines of treatment is limited, which translates into an unfavorable prognosis. This explains the need to search for new therapeutic targets to improve treatment results [18].

Epigenetic therapies

A properly functioning SWI/SNF complex has an antagonistic effect on the repressor function of the PRC1 and PRC2 protein complexes in the regulation of gene expression. Loss of function of the SWI/SNF complex leads to increased PRC2 activity with a simultaneous increase in the level of H3K27me3 [3,13,28,14]. Abnormal PRC2 function may promote oncogenesis by repressing tumor suppressor genes, including CDKN2A. Cancer cells with a pathogenic mutation of the SMARCA4 gene are sensitive to the suppression of EZH2 (enhancer of zeste homolog 2) the catalytic subunit of PRC2, responsible for transcriptional repression through trimethylation of lysine at position 27 of histone H3. In the SCCOHT cell model, inhibition of EZH2 (EPZ-6438 inhibitor) induces re expression of the SMARCA2 gene, expression of neuronal cell-specific proteins, cell cycle inhibition in the G1 phase, and apoptosis. Moreover, re expression of the SMARCA4 gene in the SCCOHT cell model resulted in a reduction in the levels of EZH2 and H3K27me3 [9]. Analogous observations were obtained when examining the effect of exposure of EPZ-6438 and GSK126 (EZH2 inhibitors) on the SCCOHT xenograft in a mouse model. A significant suppression of tumor growth and an extension of the median survival were found with moderate side effects compared to the control group [29]. The above data indicate a close correlation between SMARCA4 gene mutation and the function of the PRC2 complex in SCCOHT cells.

A phase I/II clinical trial (NCT02601950) evaluating the effect of the EZH2 inhibitor tazemetostat (EPZ-6438) demonstrated disease stabilization in one case of SCCOHT and a partial response in the other [30]. However, the trial using tazemetostat was suspended due to the observed secondary lymphomas [6,29].

So far, clinical trials with the histone deacetylase inhibitor (HDACi) quisinostat (showing affinity primarily for HDAC1 and HDAC2) have yielded promising results in resistant cutaneous T-cell lymphoma and selected solid tumors. The effect of quisinostat on SCCOHT cell lines (COV434, BIN 67, SCCOHT-1) was also assessed. Exposure of SCCOHT cells to sublethal doses of quisinostat inhibited their growth in a time-dependent manner and reduced the ability to form colonies. Low doses of quisinostat (5 nM) induced cell cycle arrest in the G1 phase, while higher doses (20, 50 nM) induced apoptosis of all SCCOHT cell lines tested in a time- and dose-dependent manner. Cells that retained vital functions after exposure to high doses (50 nM) exhibited bipolar and elongated morphology. The chronic effect of quisinostat at a dose of 10 nM on SCCOHT cells resulted in their dedifferentiation towards neuronal cells. Proteome analysis using mass spectrometry after exposure to quisinostat showed a significant increase in the concentration of CDKN1A and the pro-apoptotic protein Bak1 in a time-dependent manner. Moreover, there was a time-dependent suppression of c-Myc expression, as well as an increase in the concentration of cleaved PARP, which indicates the arrest of the cell cycle and the induction of the apoptosis process. Then, the effect of quisinostat was analyzed in mouse xenograft models. Administration of quisinostat for 3 weeks at both 10 mg/kg/day and 20 mg/kg/day to mice implanted with BIN67 cells resulted in a significant reduction in tumor mass compared to the control group with good treatment tolerance without loss of body weight [4,7,16].

Mice implanted with SCCOHT-1 cells, which show much greater sensitivity to quisinostat in vitro, received a drug dose of 5 mg/kg/day (recommended dose for humans). Although a slowdown in tumor growth was observed, all SCCOHT-1 models tested showed progression during three weeks of treatment. The above result indicates that the administration of quisinostat at a dose of 5 mg/kg/day can suppress, but not completely stop, the increase in SCCOHT. Next, the hypothesis was verified whether simultaneous inhibition of EZH2 and HDAC show synergistic action. The combined administration of quisinostat with EPZ-6438 caused apoptosis of BIN67 and COV434 cells in a shorter time than in the case of administration of each of the above drugs in monotherapy [29]. Similar results, supporting synergism of action, were obtained with the combined use of other selected drugs from the groups of EZH2 and HDAC inhibitors [31].

The effect of combined treatment with the above regimen was also demonstrated in a mouse model of the BIN67 xenograft

line. It was shown that the administration of suboptimal doses of quisinostat (5 mg/kg/day) with EPZ-6438 (200 mg/kg/day) completely stopped tumor growth during three weeks of treatment, alongside the observation of slight weight loss. However, after discontinuation of drug administration, tumor regrowth was found with a volume doubling time similar to that of the control group. The median survival time was extended to 70 days in the study group, compared to 44.5 days in the control group. Therefore, the above observations justify the perception of EZH2 and HDAC inhibitors as a promising method of treating SCCOHT, primarily in the context of combination therapy [17,29,32,33].

Lysine-specific histone demethylase 1 (LSD1) is an epigenetic enzyme involved in the regulation of gene expression. Abnormal activity is associated with oncogenesis as well as the progression of many types of cancer, and increased levels correlate with the aggressive course of the disease. LSD1 also promotes tumorigenesis by demethylation of non-histone substrates, among others p53 protein, E2F1, DNMT1. The effect of the reversible LSD1 inhibitor SP-2577 (Seclidemstat) on ovarian cancer cell lines with a mutant SWI/SNF complex was assessed. The authors found that the abnormal SWI/SNF variant correlates with high LSD1 activity, the inhibition of which inhibits cell proliferation. SCCOHT cell lines (COV434, BIN 67, SCCOHT-1) exposed to SP-2577 presented increased expression of endogenous retroviruses (ERVs), IFN-β, interferon-induced chemokine CXCL10, demonstrating activation of the interferon-dependent immune response. Increased secretion of cytokines has also been demonstrated, including: IL-1β, IL-2, IL-8 by the tested SCCOHT cells, inducing migration and infiltration of peripheral blood mononuclear cells (PBMCs). Subpopulations of PBMCs exhibiting chemotactic activity were then analyzed, concluding that the action of SP-2577 on SCCOHT cells promotes their infiltration by T and NKT cells, which consequently leads to cytotoxicity [28].

As previously proven, LSD1 plays a key role in the epigenetic silencing of PD-1 expression, while its suppression increases PD-L1 expression in cancer cells. In the same work, it was shown that SCCOHT cells under the influence of SP-2577 show significantly increased PD-L1 expression [28,34]. Moreover, the addition of anti-PD-L1 antibodies resulted in a significant increase in infiltration by PBMCs, and the combination of anti-PD-L1 antibodies with anti-CTLA-4 intensified the observed effect. Next, a hypothesis was put forward whether reexpression of SMARCA4 in SCCOHT cells, while restoring the proper function of the SWI/SNF complex, would affect the infiltration by PBMCs observed after exposure to SP-2577. Obtaining the proper function of the SWI/SNF complex by re-expressing the SMARCA4 gene in SCCOHT cells previously exposed to SP-2577 resulted in a significant reduction in infiltration by PBMCs, suppression of the expression of ERVs, IFNβ, the interferon-stimulated gene ISG15 and PD-L1 in relation to the control line. The above observations confirm that epigenetic modifications of gene expression significantly correlate with tumor immunogenicity. The use of SP-2577 in combination with ICB is a potential strategy for the treatment of SCCOHT and possibly other cancers with a pathogenic variant of SWI/SNF, nevertheless requiring evaluation of effectiveness in clinical trials [28].

CDK4/6 inhibitors

SCCOHT cells have been shown to be highly sensitive to CDK4/6 inhibition in vitro and in vivo. Loss of SMARCA4 gene function causes a significant reduction in the activity of cyclin D1, which under normal conditions has a suppressive effect on CDK4/6 kinase. It has been shown that ectopic expression of cyclin D1 in SCCOHT cells leads to an increase in RB protein phosphorylation and resistance to CDK4/6 inhibition, while inhibition of expression sensitizes these cells to the action of palbociclib [34]. SCOOHT cell lines exposed to palbociclib had a similar or lower IC50 index compared to estrogen-dependent breast cancer cell lines. A similar effect was observed with abemaciclib and ribociclib. Studies conducted on mouse models of the SCCOHT xenograft, as well as on a patient-derived xenograft, yielded the same results. Subsequently, immunohistochemical tests revealed a decrease in the mitotic index, Ki67 expression and RB protein phosphorylation in the tumor tissue after palbociclib treatment. A similar effect was found after exposure of non-small cell lung cancer cells with SMARCA4 gene mutation to CDK4/6 inhibitors. The frequency of SMARCA4 gene mutations in various types of cancer, as well as the observed effectiveness of CDK4/6 inhibitors, justify the perception of the implementation of cyclibs in the therapy of cancers with a pathogenic variant of the SMARCA4 gene as a promising treatment strategy [16,35].

Tyrosine kinase inhibitors

Ponatinib is a multikinase inhibitor used in the treatment of chronic myeloid leukemia and acute lymphoblastic leukemia. The effectiveness of this drug in relation to SCCOHT was assessed both in vitro and in vivo. SCCOHT cell lines were on average 9 times more sensitive to ponatinib compared to ovarian cancer cell lines with a functional SWI/SNF complex. Moreover, reexpression of the SMARCA4 gene induced resistance to ponatinib. It has been demonstrated, that the main therapeutic targets in SCCOHT cells are the signal transduction pathways related to PDGFRA and FGFR1, demonstrating the reduction of phosphorylation of p38, Akt S473 and Akt T308 proteins after exposure to ponatinib. Treatment response was then assessed in the SCCOHT xenograft animal model. The administration of ponatinib to mice previously implanted subcutaneously with SCCOHT cells resulted in a significant slowdown in the doubling of tumor volume and an improvement in median survival by 44% compared to the control group. Similar results were obtained when examining the effect

of ponatinib on two models of patient-derived xenografts PDX-465 and PDX-040. After 30 days of ponatinib administration, a statistically significant reduction in tumor size was found by 58.6% and 42.5%, respectively, which turned out to be consistent with the reduction phosphorylation of kinases in each model. Under exposure to ponatinib, significant suppression was demonstrated, but no complete inhibition of SCCOHT growth was observed [27].

Immunotherapy

SCCOHT is characterized by an extremely low mutational burden (Total Mutational Burden - TMB), which does not support the consideration of immunotherapy as a potential treatment option. Nevertheless, the research results reported so far indicate that the presence of mutations in the subunits of the SWI/SNF complex resulting in the loss of its function correlates with the increased expression of immune checkpoint regulators [3]. Consequently, despite low TMB, SCCOHT presents biologically significant immunogenicity, PD-L1 expression, and infiltration by PMBCs [36]. Despite initially promising results with ICB, durable responses were observed in a minority of patients with SCCOHT. Moreover, disease progression through acquired drug resistance turned out to be a common phenomenon. Isolated reports report a durable response after the use of pembrolizumab in a selected group of patients with recurrent SCCOHT previously treated with chemotherapy followed by radiotherapy.

Positive results of SCCOHT treatment were achieved by combining CDK4/6 inhibitors with immune checkpoint inhibitors. The above observation is consistent with the results of preclinical studies on cellular models of melanoma and clear cell renal cell carcinoma with afunctional SWI/SNF complexes. Based on previous reports, more favorable clinical responses with ICB are achieved through combination therapies. A single case report presented by Li G et al. demonstrates benefit of use combined treatment with camrelizumab (anti-PD-1) and apatinib in a patient with progression of SCCOHT after two lines of chemotherapy followed by radiotherapy to the area of enlarged retroperitoneal lymph nodes [33]. After 4 cycles (camrelizumab 200 mg i.v. q3w, apatinib 250 mg p.o. daily) a partial response was achieved. The drug administration regimen was continued for 2 years with continued partial response and good treatment tolerance. Preparations with antiangiogenic activity increase tumor infiltration by immune system cells and, by influencing the tumor microenvironment, increase the effectiveness of ICB use. The synergistic effect of ICB and antiangiogenic drugs was confirmed by the KEYNOTE-426 study (pembrolizumab + axitinib vs. sunitinib in the first-line treatment of advanced RCC) and JAVELIN Renal 101 (avelumab + axitinib vs. sunitinib in advanced RCC) [37].

In view of the effectiveness of treatment in the above case, radiotherapy performed before the implementation of immunotherapy is important. Based on clinical studies to date, better responses to treatment have been demonstrated in the group of patients who received radiotherapy before the implementation of ICB compared to patients receiving only ICB. It is believed that exposure of tumors to radiation promotes the release of additional antigens, which in turn enhances the antitumor effects of T cells [18,25].

BET/MEK Inhibitors

The BRD4 protein, belonging to the BET protein family, contains a bromodomain responsible for recognizing acetylated lysine residues in nucleosomes, and participates in the promotion of gene transcription. Shorstova et al. put forward a hypothesis that in the absence of the BRG1 protein encoded by the SMARCA4 gene, BRD4 may play a key role in the mechanism of gene transcription, determining cell proliferation and survival. Therefore, inhibition of BET family proteins should effectively inhibit the process of oncogenesis dependent on them. It was then shown that SCCOHT and non-small cell lung cancer cell lines (with SMARCA4 gene mutation) are significantly sensitive to BET inhibitors in vitro. The above observations were also confirmed in vivo by exposing mouse models to low concentrations of BETi. The effectiveness of BETi correlates with the repression of PI3K and MAPK signaling pathways. This is consistent with the phenomenon of BETi resistance under conditions of constitutive activation of the PI3K and MAPK pathways. Cells with preserved SMARCA4 expression are largely insensitive to the influence of BETi, showing no reduction in PI3K and MAPK activity. Guided by the potential synergy of drug action and the intention to overcome possible resistance to BETi, the authors analyzed the effectiveness of selected PI3K and MAPK pathway inhibitors in combination with BETi in relation to murine xenografts of specific ovarian cancer lines, both showing SMARCA4 mutations (SCCOHT-1 and OVK18) as well as with the normal gene variant (OVCAR4, OVCAR3, SCOV3 and IGROV1). The OVK18 cell line is characterized by relative resistance to BETi, probably caused by the A59G mutation of the KRAS gene. The most effective synergy was found when used together in suboptimal doses of BETi (OTX015) with MEK inhibitors - cobimetinib and trabetinib, regardless of SMARCA4 mutation status [35]. Clinically, the tested mice showed a reduction in tumor growth, good tolerance of the treatment, without obvious symptoms of toxicity or weight loss. Using mass spectrometry, it was demonstrated that the above BETi/METi combination causes repression of key enzymes involved in nucleotide metabolism, reduction of the pool of their precursors necessary in the DNA synthesis process, and, consequently, cell cycle arrest [14,35].

Arginine elimination

Arginine is an endogenous amino acid, a metabolite of the urea cycle, which participates in many biosynthetic pathways. Most healthy human cells have the ability to synthesize arginine

using two enzymes of the urea cycle - argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL). The level of ASS expression varies between different types of cancer. The presence of arginine in the environment determines the survival of cancer cells that do not exhibit ASS enzymatic activity and are auxotrophic towards this amino acid. ADI-PEG20 is a pegylated form of arginine deiminase - an enzyme of bacterial origin that effectively decomposes arginine.

Currently, there are phase 1-3 clinical trials assessing the effectiveness of the treatment, including – melanoma, hepatocellular carcinoma, or mesothelioma. In the study by Ji X, et al. the level of ASS enzymatic activity of selected ovarian cancer subtypes was analyzed (endometroid - ENOC, clear cell - CCOC, small-cell hypercalcemic - SCCOHT, high-grade serous - HGSC). HG serous carcinoma cells had the highest level of expression. It should be noted that low ASS expression in HG serous carcinoma cells correlates with platinum resistance. SCCOHT cells had uniformly low ASS activity, and reexpression of the SMARCA4 gene was unrelated to the ASS level. ENOC and CCOC showed different levels of ASS expression. Further molecular and immunohistochemical studies in a broader ENOC cohort confirmed the correlation between CTNNB1 gene mutation and low ASS expression. The authors then demonstrated that exposure of cell lines with low or no ASS expression to ADI-PEG20 causes inhibition of their growth and apoptosis, regardless of the subtype of ovarian cancer. Moreover, ADI-PEG20 caused a decrease in the colony-forming potential in cell lines with preserved ASS expression and a complete loss of the colony-forming ability of cells without ASS activity in relation to the control groups. Next, to evaluate the effect of ADI-PEG20 in vivo, mouse models with subcutaneous implantation of SCCOHT cells and a mouse model of patient-derived SCCOHT xenograft were used [38].

The supply of ADI-PEG20 at a dose of 15 mg/kg and 30 mg/kg every week for 4 weeks significantly reduced the tumor size compared to the control group. However, intolerable treatment toxicity was observed in individual cases in the 30 mg/kg/week group. A reduction in the level of Ki67 and the mitotic index was found in the examined tumors, however, persistent focal IHC staining for Ki67 was also visible in tumor cells exposed to a dose of 30 mg/kg/week. Furthermore, the examined SCCOHT material showed focal small areas of ASS reexpression in both the experimental and control groups, implying resistance to therapy [38].

In summary, ADI-PEG20 induces a significant response of ASS-deficient cells, manifested by inhibition of their growth and apoptosis. It is also a potential treatment strategy for SCCOHT, and combination therapy with ADI-PEG20 may result in measurable benefits in clinical practice. Recent clinical trials combining ADI-PEG20 with conventional chemotherapy have yielded promising results in the group of gastrointestinal cancers and pancreatic cancer, regardless of ASS status. Currently, there are no clinical trials using ADI-PEG20 in patients with ovarian cancer.

Discussion

SCCOHT is an extremely aggressive and rare cancer that primarily affects young women. Despite significant progress in diagnostics and treatment methods, the prognosis remains unfavorable. Immunohistochemical testing for SMARCA4 mutations is not part of routine pathological diagnosis, and the immunohistochemical profile of SCCOHT cells obtained with standard staining does not show pathognomic features constituting the basis for the diagnosis. As a result the morbidity described at the beginning should be considered underestimated, and given the young age and frequent lack of comorbidities among SCCOHT patients, a lower rate of unacceptable treatment toxicity can be expected. The reports presented in this article allow us to expect measurable benefits in clinical practice resulting from the development of new treatment methods, including combination therapies.

It is important that approximately 20% of all cancers have a defective SWI/SNF variant (acquired at various stages of oncogenesis), thus equaling the frequency of the abnormal TP53 protein. Ten to thirty seven percent of non-small cell lung cancer cases show loss of SMARCA4 gene expression and approximately 10% of melanoma cells. SCCOHT, considering its extremely low TMB, diploid karyotype and microsatellite stability, is therefore an optimal model for research on the importance of epigenetics in oncogenesis. Identification of therapeutic targets based on the SCCOHT model, characterized by a low mutational burden on the genome, may potentially define new strategies for the treatment of many cancers showing abnormal function of the SWI/SNF complex.

Conclusion

SCCOHT is an extremely rare cancer with a very aggressive course, affecting very young women whose survival, with currently used therapeutic methods, does not exceed 24 months from diagnosis. Due to its rare occurrence and, therefore, the impossibility of conducting randomized trials, information about postoperative management is based on individual reports in the literature. The search for new therapies based on the assessment of genetic and immunohistochemical factors is necessary to improve the survival of this group of patients.

Disclosure

Ethical Considerations: Ethical approval and informed consent statements for research involving humans or animals were not needed for the current manuscript.

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