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ABSTRACT

Globally, endometrial cancer (EC) is the six most common cancers related to female reproductive. EC incidence and mortality rates have increased over the last decade. Cytotoxic therapy with carboplatin or paclitaxel is the recommended first-line treatment for EC patients. However, the options for following therapy are limited. The latest advances in molecular studies have uncovered the nature of genetic alterations in EC, compelling methods for further research into the treatment of EC since they may disclose to tailored pharmacological therapy. The aim of this study was to identify novel drug candidates in treating EC using genomics variants and biological pathway. The genomic variants of EC were downloaded from cBioportal database. We established connection between the biological EC risk genes from cBioportal database and the DrugBank database. Finally, we used Connectivity Map (CMap) analysis to identify possible drugs whose mechanisms coincided with therapeutic targets and rank them in accordance to scoring criteria. We identified novel conceivable candidate drugs for EC, they are Bosutinib, Acitretin and Nilutamide. These drugs exhibit robust scores in the CMap analysis compare to paclitaxel. We also discovered BCR-ABL1 and AR as potential biomarker-driven therapy in EC. This study demonstrates the possibility of using genetic network analysis combined with bioinformatics to repurpose drugs for the treatment of EC. Further investigation will be undertaken to explore the mechanisms involved in the application of BCR-ABL1 and AR for treating of EC.

Keywords: acitretin, bosutinib, drug reporpusing, endometrial cancer, genomics variants, nilutamide

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INTRODUCTION

Endometrial cancer (EC) refers to the uncontrolled growth of cancer cells originating from the endometrium, the innermost epithelial lining of the uterine (Society, 2023) . In the past few years, there has been growing concern among gynecologic-oncologists regarding the increasing incidence and mortality rates of EC annually (Lu & Broaddus, 2020). Globally, EC ranks as the sixth leading common cancer among female, approximately 417,000 current cases and 97,000 mortality recorded in 2020 with obesity, sedentary lifestyle, declining of hysterectomy and birth control as the risk factors (Lortet-Tieulent et al., 2018; Sung et al., 2021; Zhang et al., 2019). According to the American Cancer Society (ACS), there were 66,200 newly diagnosed resulting 13,030 fatalities attributed to EC in 2023. It represents an increase compared to their 2015 report, which recorded 54,870 new cases and 10,170 deaths (Siegel et al., 2015, 2023).

Based on data from the US Surveillance, Epidemiology, and End Results (SEER) report between the years 2011 and 2017, the five-year overall survival of EC is approximately 81.1%. The survival rates for early stage, moderate stage, and advanced stage EC are reported as 94.9%, 69.3%, and 17.8%, respectively. These findings indicate that the prognosis for late-stage EC is indigent. Moreover, there are restricted therapeutic options available for late-stage and recurring EC (Mahdi et al., 2023). First line therapy using carboplatin or paclitaxel is challenging due to the toxicity as well as the hetergenous type of EC (Knisely et al., 2022; Mahdi et al., 2023), highlighting the need of personalized therapies as a potential treatment approach in EC (Connor & Rose, 2018).

Traditionally, EC is categorized into two types, which are determined by histological subtype, the expression of sex hormone receptors, and the grade of the tumor. Type 1 called endometrioid type is approximately 80% cases and low grade type of EC. Whereas, type 2 called estrogen-dependent or non-endometrioid type approximately 20% of cases and advanced grade (Lu & Broaddus, 2020; Morice et al., 2016). In 2013, The Cancer Genome Atlas (TCGA) Research Network was able to describe endometrioid carcinoma, endometrial serous carcinoma, and carcinosarcoma into 4 molecular classifications. They are ultramutated DNA polymerase epsilon (POLE), hypermutated microsatellite instable (MSI), copy-number low (CNL) and copy-number high (CNH) (Levine, 2013). Patients with POLE mutations in EC exhibit a notably elevated frequency of mutations, leading to an extreme mutation burden referred to as ultramutated. Notably, this group displays significantly extended survival rates. Another distinct cluster consists of EC patients with MSI and a high mutation load, predominantly comprising type 1 EC cases. Although their mutation burden is lower compared to the ultramutated group, it remains significantly elevated. Additionally, EC patients with CNL are primarily diagnosed with endometrioid carcinomas displaying microsatellite stability (MSS). Conversely, EC patients with CNH, known as endometrial serous carcinomas, exhibit low mutation rates, frequent copy-number alterations, and TP53 mutations (Levine, 2013). Therefore, this genomics-based classification open a new opportunity to develop a novel genomics-based drug repurposing.

Recently, the concept of repurposing drugs in diseases is gaining interest due to the time-consuming and costly nature of discovering novel drugs (Pushpakom et al., 2019). By utilizing genetic associations, pathway mapping, and phenotypic screening, it is possible to identify potential repurposing candidates. With the completing of the Human Genome Project and decreasing costs of sequencing techniques, genome-wide association studies (GWAS) have advanced the field by identifying genetic variants associated with common diseases such as tuberculosis (Irham et al., 2022), asthma (Adikusuma et al., 2022; Santri et al., 2022) multiple sclerosis (Afief et al., 2022), and chronic hepatitis B (Irham et al., 2022). Drugs has been reporting to treat gynecological cancers as drug repositioning strategies, such as Metformin, Vorinostat, Tranilast, PPAR ligands and COX-2 inhibitors (Banno et al., 2015; Irie et al., 2016; Torricelli et al., 2023; Watanabe et al., 2023). Metformin was found effective for EC by inhibiting PI3K-Akt-mTOR pathway (Banno et al., 2015; Irie et al., 2016). In addition, Quinacrine already proved preclinically (Kalogera et al., 2017), Letrozole had a durable outcome when combine with abemaciclib in phase-II clinical trial (Konstantinopoulos et al., 2023) and metformin had a survival benefit in EC patients in retrospective cohort study (Ezewuiro et al., 2016). In the present study, we examined genetic variations and incorporated them into an analysis of

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biological pathways. The aim was to discover a potential target for repurposing existing drugs in the context of EC.

MATERIALS AND METHOD

Obtaining endometrial cancer associated genes

Workflow of the current drug repurposing study in EC is shown in Figure 1. The cBioPortal database (https://www.cbioportal.org/), accessed on May 8, 2023, was employed to identify genes associated with EC that exhibit somatic mutations, referred to as EC-associated genetic variants. The cBioPortal serves as an extensive and openly accessible repository for cancer genomics data, comprising over 5,000 tumor specimens from 20 unique cancer experiments (Cerami et al., 2012). These genetic variants extracted from the cBioPortal can be leveraged to derive biological insights and inform therapeutic applications in the field of cancer genetics.

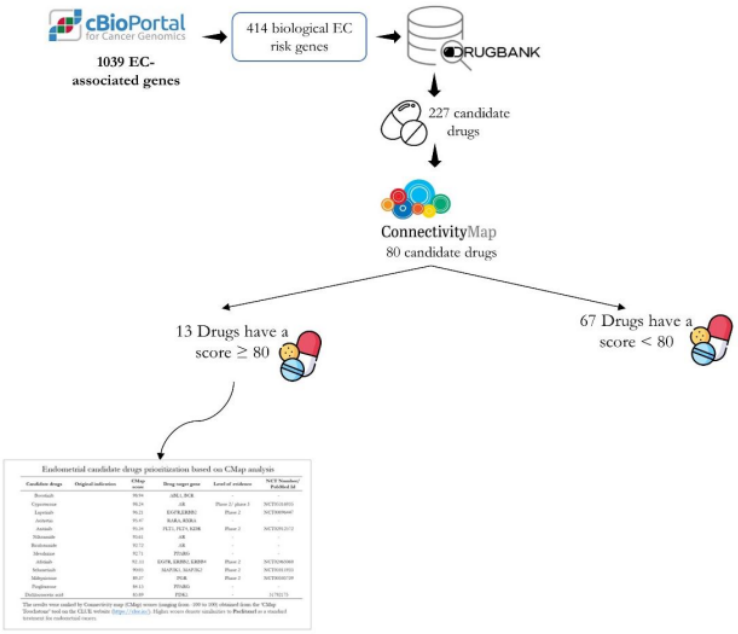

Figure 1. Workflow of drug repurposing for endometrial cancer (EC). The study design utilizing by cBioportal, DrugBank, and CMap database. Six distinct criteria were applied in this study, such as (i) Biological process (BP), (ii) Cellular component (CC), (iii) Molecular functions (MF), (iv) Knockout mouse phenotype (KO_Mouse), (v) Kyoto encyclopedia of genes and genomes (KEGG), and (vi) Primary immunodeficiency (PID) 2019

Uncover genes implicated in the biological risk of EC

In order to identify genes that confer a biological risk for EC, six distinct criteria were applied in this study: (i) Biological process (BP), (ii) Cellular component (CC), (iii) Molecular functions (MF), (iv) Knockout mouse phenotype (KO Mouse), (v) Kyoto encyclopedia of genes and genomes (KEGG), and (vi) Primary immunodeficiency (PID) 2019. As mentioned in the previous study (Irham et al., 2022), genes that met or exceeded a score of 2 based on these criteria were designated as biological EC-risk genes, with a higher score indicating a more substantial influence on EC pathogenesis. The

functional enrichment analysis tool WebGestalt 2019 was utilized to evaluate the first five criteria (BP, CC, MF, KO_Mouse, and KEGG) on May 8, 2023 (Liao et al., 2019). The PID data were subjected to an enrichment analysis employing a hypergeometric test, where a *p*-value of 0.05 or less was considered statistically significant. BP, CC, and MF are gene ontology (GO) criteria that were annotated to decode protein-protein interaction, while KO_Mouse was utilized to determine whether a gene was linked to a specific phenotype in mice, and KEGG was used to determine which genes impacted the molecular pathway. Lastly, genes found in PID were prioritized to identify biological EC risk genes, given that EC is an immune disease. The IUIS Phenotypical Classification 2019 Update was used to gather PID genes (Bousfiha et al., 2020).

Analyze and integrate data to explore drug repositioning possibilities for EC

In order to identify potential candidate drugs for EC, a connection was established between the biological EC risk genes and the DrugBank database (version 5.1.10, released on January 4, 2023), considering various criteria. These criteria included drugs suitable for human use, drugs with a specific mode of action, and drugs targeting particular genes. The DrugBank database, a user-friendly online resource, offers comprehensive information on drugs and their targets, thus provide as a relevant tool for drug discovery (Wishart et al., 2018). Next, for prioritizing potential candidate drugs for EC, CMap touchstone (CMap Ts) analysis was employed, utilizing the CMap TS database accessed via https://clue.io/ on February 2, 2023. The prioritization process involved ranking drugs based on a connection score ranging from -100 to 100 (Subramanian et al., 2017). The CMap TS database consists of information on the influence of different pharmaceutical agents on the gene expression profile of human cancer cells, thereby aiding in the identification of new applications for existing drugs. The database contains connections between approximately 3,000 drugs and changes in approximately 20,000 genes across different cell lines. This study focused on nine specific types of human cancer cells (A375, A549, HA1E, EC515, HEPG2, MCF7, PC3, VCAP, and HT29) to analyze the effects of drugs (Lamb et al., 2006). By examining the drugs effects on gene expression in the cells, the researchers aimed to identify drugs that may have efficacy beyond their intended purpose. In this study, the goal was to discover new treatments for EC by comparing the effects of different drugs, including the commonly used EC treatment Paclitaxel.

RESULT AND DISCUSSION

Assigning priority to genes associated with EC

To identify specifically relevant targets in EC, we utilized the cBioPortal database (https://www.cbioportal.org/), which provided access to seven research papers containing EC-related data. A total of 1,954 patients participated in these trials **(Table S1)**, resulting in the identification of 1,530 mutated genes associated with EC. However, the analysis focused exclusively on the 1,039 genes exhibiting the strongest evidence linking them to the disease **(Table S2)** based on mutation frequency of 1% or higher. Subsequently, 1,039 genes underwent prioritization using six functional annotations, leading to the following outcomes: (i) 345 genes prioritized based on biological processes (BP), (ii) 231 genes prioritized based on cellular components (CC), (iii) 231 genes prioritized based on molecular functions (MF), (iv) 186 genes prioritized based on the Kyoto Encyclopedia of Genes and Genomes (KEGG), (v) 310 genes prioritized based on knockout mouse phenotypes (KO_Mouse), and (vi) 69 genes prioritized based on primary immunodeficiency (PID) **(Table S3)**. We identified 393 genes received a score of 0, 232 genes received a score of 1, and 414 genes obtained a total score of ≥ 2. Consequently, these 414 genes met the cutoff value of 2 and were assigned as "Biological EC risk genes." This study conducted an in-depth analysis of the distribution scores of functional annotations and genes based on the six criteria, with the corresponding results depicted in Figure 2. Remarkably,

the findings emphasized that increased annotation scores are indicative of a greater influence of genes on diseases.

Gene	Gene Ontology			KEGG	PID	KMP	Total score
	BP	CC	MF				
JAK3	1	1	1	1	1	1	6
RAC2	1	1	1	1	1	0	5
KRAS	1	1	1	1	0	1	5
FGFR2	1	1	1	1	0	1	5
MTOR	1	1	1	1	0	1	5
ALK	1	1	1	1	0	1	5
PIK3CB	1	1	1	1	0	1	5
MET	1	1	1	1	0	1	5
KIT	1	1	1	1	0	1	5
EGFR	1	1	1	1	0	1	5
ABL1	1	1	1	1	0	1	5
PDGFRB	1	1	1	1	0	1	5
BRAF	1	1	1	1	0	1	5
CSF1R	1	1	1	1	0	1	5
AKT1	1	1	1	1	0	1	5
RUNX1	1	1	1	1	0	1	5
AKT2	1	1	1	1	0	1	5
NRAS	1	1	1	1	0	1	5
CDK6	1	1	1	1	0	1	5
CDK4	1	1	1	1	0	1	5
HRAS	1	1	1	1	0	1	5
ATM	1	1	1	0	1	1	5
PIK3CG	1	1	1	0	1	1	5
BRIP1	1	1	1	0	1	1	5
JAK1	0	1	1	1	1	1	5
PIK3CD	0	1	1	1	1	1	5

Figure 2. Gene-based prioritization from functional annotation. BP: biological processes; CC: cellular components; MF: molecular functions; KEGG: Kyoto Encyclopedia of Genes and Genomes; KMP: knockout mouse phenotypes (KO_Mouse); PID: primary immunodeficiency; EC: endometrial cancer

Drug target gene overlapped with DrugBank

We identified a total of 414 genes associated with an increased risk of EC risk genes in the biological context. These genes were carefully selected as the definitive list of candidate genes for subsequent in-depth analysis. We then systematically aligned the above 414 drug target genes with entries in the DrugBank database using a number of specific criteria. These criteria included considerations of pharmacological activity, human efficacy, and annotations indicating the approval status, ongoing clinical trials, or experimental nature of the associated drugs. A critical observation to emphasize is that not all of the identified drug target genes have the potential to be effectively targeted by drugs (druggable). In the initial pool, only 82 of the drug target genes showed the ability to interact with 227 different drugs (**Table S4**). This subset of genes and drugs exemplifies cases where the potential for therapeutic intervention matches the genetic and pharmacological landscape. We found androgen receptor (AR), breakpoint cluster region (BCR), epidermal growth factor receptor (EGFR), retinoid X receptor alpha (RXRA) and kinase insert domain receptor (KDR) as 5 top drugable target genes. Meta-analysis studies found that AR expression as a favorable prognostic indicator and imparts a preferable survival outcome of EC patients (Wu et al., 2022). Recent study also found that AR expression was notably strong in 85% of EC and suggested could become a potential targeted therapy in the future (Moatamed et al., 2023). In addition, BCR-ABL1 is one of the six genes identified involved in metastatic EC and overexpression of BCR-ABL1 gene was in line with a poor survival rate of EC patients (Ajabnoor et al., 2023).

Identification of a potential drug candidate for the therapy of endometrial cancer as per CMap analysis

In order to systematically rank the most prospective drugs for potential therapy in EC, we comprehensively evaluated 227 drugs from the CMap Touchstone directory. We employed the

molecular signatures of paclitaxel as a baseline standard for EC treatment. Importantly, a subset of 80 drugs showed positive correlations with the profiles of paclitaxel, indicating potential therapeutic relevance. The subsequent ranking process involved evaluating all 80 drugs based on their respective scores in the CMap Touchstone directory. We subsequently identified 13 drugs with scores exceeding 80 as prime candidates for EC treatment, as outlined in Table 1. Out of the 13 curated agents from the CMap Touchstone database, noteworthy observations emerged: six of them are currently undergoing clinical trials for a different condition, namely EC. The drugs in question are Cyproterone, Lapatinib, Axitinib, Afatinib, Selumetinib, and Mifepristone. Dichloroacetic acid has undergone preclinical investigations. Furthermore, Bosutinib, Acitretin, Nilutamide, Bicalutamide, Mesalazine, and Pioglitazone lack concrete evidence from clinical trials. Figure 3 visually illustrates the interconnection between the target proteins, EC's candidate drugs, and their corresponding levels of evidence. Bosutinib, Acitretin, and Nilutamide which exhibit robust scores in the CMap analysis, draw specific attention within this set of 13 drugs. The elevated scores of these three drugs show a considerable signify as potential candidates in repurposing therapy of EC.

Bosutinib is known as tyrosine kinase inhibitor (TKI) that targeted ABL tyrosine kinase, (specifically their catalytic activity) and was encoded by ABL1 (Massimino et al., 2020). ABL1 was reported as a potential gene involved metastasis in EC and might be as a potential drug gene in EC (Ajabnoor et al., 2023). Acitretin is a second generation retinoid that has antitumor activity as 10dication for several carcinoma (Zhao et al., 2021). Acitretin as a retinoid acid is mediated by retinoic acid receptor (RAR) and retinoic X receptor (RXR) (Hunsu et al., 2021). Previous studi reported that retinoic acid receptor alpha (RARA) was associated with poor overall survival in EC patient (Lu & Broaddus, 2020). Nilutamide, AR inhibitor is an oral non-steroidal agent that binded and inhibited AR (Reichert & Hussain, 2016; Sharma & Hwa, 2021). Moreover, AR found as a prognostic marker in EC and highest level of AR was associated with well-differentiated primary tumor (Tangen et al., 2016). Some studies showed that AR expression related to favorable prognostic in EC patient (Hashmi et al., 2018).

Paclitaxel was the natural first-line chemotherapy drug to treat cance11at can inhibit cell mitosis, increased the apoptosis, tumor specific antigen releasing and amplify the phagocytosis of antigen-presenting cells (APCs). Activation of APCs can release many pro-inflammatory cytokines (Zhu & Chen, 2019). Usually, paclitaxel was combined with carboplatin that was justified as the most active and tolerable chemotherapy drug (Randall et al., 2019). Advanced or recurrent EC patients treat with carboplatin and paclitaxel as the first line drugs (Ackroyd et al., 2021). Therefore, combination of bosutinib, acitretin or nilutamide with paclitaxel and or carboplatin might be a novel potential treatment option for chemtherapy-resistant EC patients. Further study is needed to investigate EC response to these drugs in vitro and *in vivo*. This study focused on bioinformatic approaches to identify drugs that may have efficacy beyond intended purpose by examining the similarities of gene expression changes caused by drugs. The advantage of this approach is to discover new treatments by prioritizing the best drug candidate for EC patients. We compare the effects of paclitaxel as a standard treatment for EC.

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Table 1. Endometrial candidate drugs prioritization based on CMap analysis

Drug candidates	Original indication	CMap score	Drug target gene(s)	Level of evidence	NCT Number/ PubMed Id
Bosutinib	Chronic myelogenous leukemia (CML)	98.94	ABL1, BCR	-	-
Cyproterone	Prostate cancer	98.24	AR	Phase 2/ phase 3	NCT05316935
Lapatinib	Breast cancer	96.21	EGFR, ERBB2	Phase 2	NCT00096447
Acitretin	Severe psoriasis	95.47	RARA, RXRA	-	-
Axitinib	Renal cell carcinoma	95.34	FLT1, FLT4, KDR	Phase 2	NCT02912572
Nilutamide	Prostate cancer	93.61	AR	-	-
Bicalutamide	Prostate cancer	92.72	AR	-	-
Mesalazine	Ulcerative colitis	92.71	PPARG	-	-
Afatinib	Non-small cell lung cancer	92..11	EGFR, ERBB2, ERBB4	Phase 2	NCT02465060
Selumetinib	Neurofibromatosis type 1	90.05	MAP2K1, MAP2K2	Phase 2	NCT01011933
Mifepristone	Pregnancy termination	89.37	PGR	Phase 2	NCT00505739
Pioglitazone	Type 2 Diabetes	84.13	PPARG	-	-
Dichloroacetic acid	Brain cancer	83.89	PDK1	-	31792175

Note: t findings were prioritized by Connectivity map (CMap) scores (ranging from -100 to 100) was acquired from the 'CMap Touchstone' tool on the CLUE website (https://clue.io/). Higher scores denote similarities to Paclitaxel as a standard treatment for EC

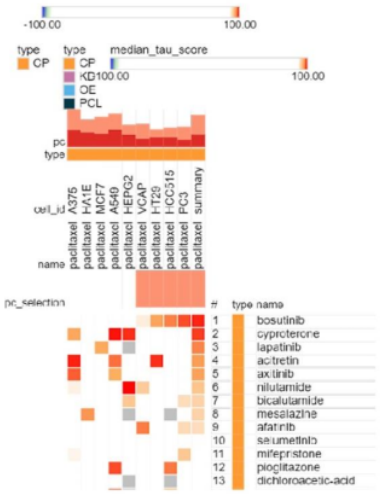

Figure 3. CMap analysis of EC's candidate drugs in cell lines using paclitaxel as standard treatment

CONCLUSION

Genomics variants database analysis discovered BCR-ABL1 and AR as the most significant biological gene risk in EC. Moreover, Bosutinib, Acitrecin and Nilutamide are the novel potential reporpusing drugs in EC.

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