Editorial

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The emerging role of JAK inhibitors in ovarian cancer: new kids on the block?

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To the Editor,

Ovarian cancer (OC) ranks as the third most prevalent gynecological cancer worldwide[1]. With an estimated 19 710 new instances in 2023 and 13 270 mortalities[2]. Unfortunately, OC diagnosis is often delayed, leading to poorer prognosis and a 17% 5-year survival rate for patients with advanced disease[1]. Although there have been advances in prevention and treatment of OC, evident by the global trend in OC cases reduction, there is a concerning increase in incidence among younger females. In addition, it remains the most lethal gynecological cancer[1,3]. Despite attempts to optimize treatment protocols, limited improvement in the overall-survival (OS) was noticed. Alarmingly, 80% of OC patients develop platinum resistance, hindering chemotherapy response rate to as low as 10–15% and resulting in an average survival of 9–12 months[4]. Such statistics warrant further research and a deeper understanding of the OC biological landscape to develop new and effective therapeutics.

A wide spectrum of genetic alternations is harbored within the biological microenvironment of OC, including *BRCA*, *TP53*, antiapoptotic proteins, and *ABCB1*. *BRCA* mutations account for 10–15% of familial OC cases. Moreover, *TP53* mutations were discovered in 60–80% of both sporadic and familial OCs[4]. In addition, OC exhibits overexpression of Bcl-2, an antiapoptotic gene, which modulates chemo-resistance and negatively influences survival[5]. Furthermore, ABCB1; a drug efflux transport that correlates with multidrug resistance, significantly contributes to chemo-resistance[6]. Notably, preclinical research highlighted the importance of the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway in OC tumorigenesis (Fig. 1). This pathway plays a vital role in cell proliferation, angiogenesis, stemness, invasion, and chemo-resistance[7].

The food and drug administration (FDA) approved of the first JAK inhibitor (ruxolitinib) back in 2011 for the treatment of myelofibrosis (MF), since then, different JAK inhibitors have been introduced[8]. Interestingly, the concept of drug repurposing has been gaining momentum, aided by the knowledge of the 'old' drugs' side effects, lower development cost, availability in the market, and lower risk of failure[9], with JAK inhibitors garnering significant attention from oncologists. Ruxolitinib is especially intriguing, with multiple preclinical and clinical studies exploring its potential repurposing. Given the promising role of JAK inhibitors in cancer and immune diseases, we write this letter, to explore the potential role of JAK inhibitors in the treatment of OCs.

Overwhelming preclinical data have elucidated that ruxolitinib promotes apoptosis in OC. It effectively reduces phosphorylated STAT3 (pSTAT3) in a dose-dependent manner and demonstrates cytotoxic activity by inhibiting cell viability. Moreover, it synergically enhances the antitumor activity of paclitaxel, cisplatin, and carboplatin. Increased apoptotic response to paclitaxel was detected when combined with ruxolitinib, accompanied by a significant reduction in Mcl-1; a prosurvival protein. This suggests that the synergistic effect arises from enhanced apoptosis. In addition, combined treatment of ruxolitinib and paclitaxel in OC xenograft models led to a noticeable reduction in tumor size[10]. Ruxolitinib combined with carboplatin induced a reduction in pSTAT3 levels in OC cells with *PBX1* overexpression and platinum resistance. Furthermore, treated tumor tissue exhibited slower tumor growth rates and smaller end tumor volumes, suggesting that targeting STAT3 activity, particularly in combination with carboplatin, effectively inhibits tumor growth and STAT3 activation in platinum-resistant OC cells with *PBX1* overexpression[11]. Between 15 and 30% of OC cases overexpress the HER2/neu oncogene. Notably, poorer prognosis was detected in patients with high expression of both HER2 and STAT3. Combined therapy involving ruxolitinib and an irreversible ErbB family blocker (afatinib) successfully increased apoptosis levels in OC cells[12]. Additionally, estrogen receptor-alpha (ERα) is expressed in 80% of epithelial ovarian cancers (EOC). However, only 20% of EOCs respond to antiestrogen therapy (AET), suggesting the presence of modifiers to response that can be targeted. Notably, cytokine release by the mesenchymal cells of OC, particularly interleukin-6/leukemia inhibitory factor (IL6/LIF), has been implicated in its tumorigenicity. The expression of IL6 correlates inversely with the response to AET and was found to induce JAK/STAT signaling. Ruxolitinib was found to block the mesenchymal cells upregulation of ERα, and the combination of ruxolitinib with the aromatase inhibitor letrozole demonstrated a synergistic cytotoxic effect *in-vitro*[13].

One active, nonrecruiting, phase I/II clinical trial (ClinicalTrials.gov identifier: NCT02713386) has been conducted to determine

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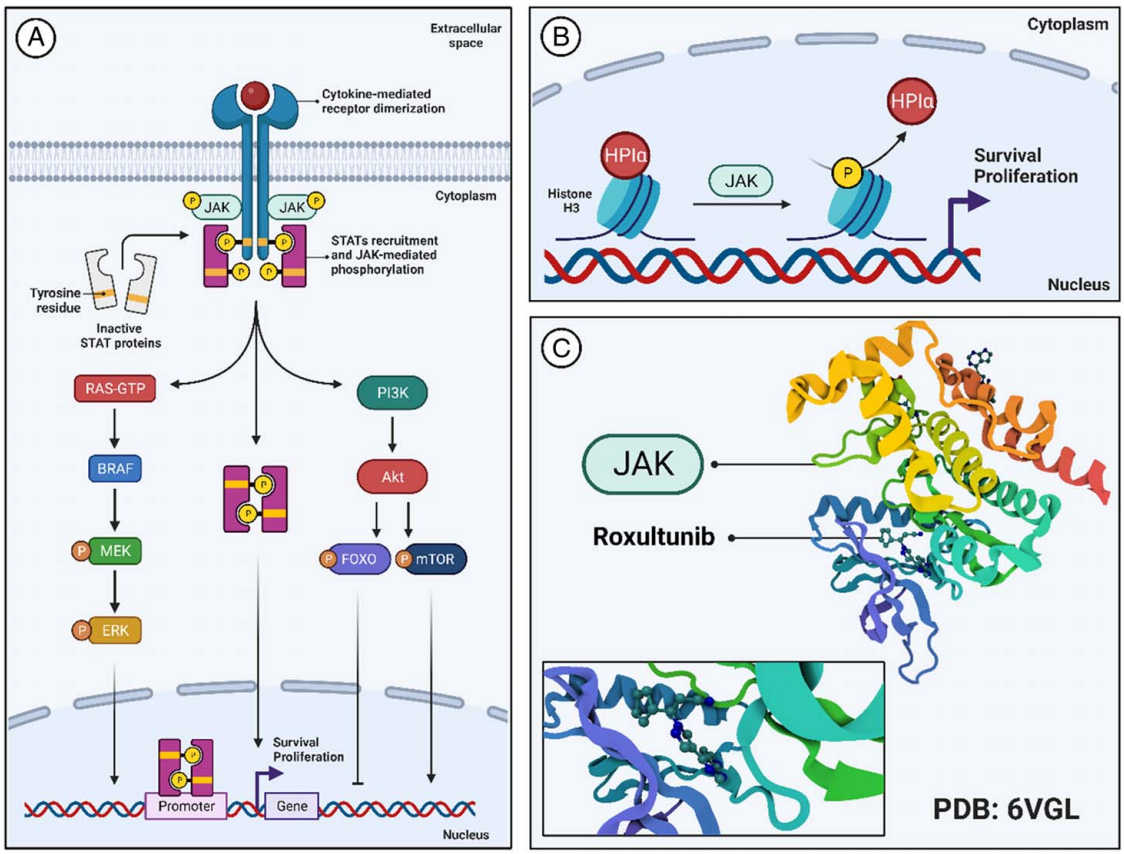

Figure 1. Schematic depiction of the JAK/STAT signal transduction. Activation and dimerization of the cell surface receptor is brought upon by cytokine binding. Activated JAK kinases phosphorylate recruited STATs. Dimerized STATs move into the nucleus and regulate the expression of specific target genes. Additionally, the activation of the JAK/STAT pathway facilitates the recruitment of the PI3K/Akt/mTOR pathway and the MAPK pathway leading to the activation of further transcription factors (A). JAK2 phosphorylates histone 3 at the Y41 region in the nucleus. Phosphorylation of H3Y41 prevents binding of the HP1α, which is a chromatin-crosslinking protein which leads to gene transcription modification (B). Three-dimensional crystal structure of JAK2 co-elucidated with ruxolitinib (PDB entry ID: 6VGL) (C). Akt, Protein kinase B; ERK, extracellular signal-regulated kinase; FOXO, forkhead box transcription factors; HP1, Heterochromatin protein 1; JAK, Janus Kinase; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; PDB, Protein Data Bank; RAS-GTP, rat sarcoma-guanosine triphosphatases; STAT, signal transducer and activator of transcription.

the optimal dose and assess side effects of ruxolitinib combined with paclitaxel and carboplatin for the treatment of stage III-IV EOC, primary peritoneal, or fallopian tube cancer. With the primary objectives of assessing the safety and tolerability of combining ruxolitinib with conventional chemotherapy for primary therapy (phase I) and to determine if this combination leads to prolonged progression-free survival (PFS) compared to chemotherapy alone (phase II). This study is an open-label trial, designed for treatment purposes, involved random allocation of participants to different treatment groups and followed an interventional model with parallel assignment. Phase I consisted of three portions, cycles 1–3, cycles 4–6, and maintenance therapy. In the first three cycles, patients received oral ruxolitinib, twice daily for the first 21 days, intravenous (IV) paclitaxel on the first, eighth, and 15th day, and IV carboplatin on day 1. Repeated for three cycles every 21 days, provided there were no unacceptable adverse effects or disease progression. Patients then underwent a tumor reductive surgery (TRS) within 6 weeks after the completion of cycle 3. Within 6 weeks after the TRS, cycles 4–6 commenced, following the same regimen used in cycles 1–3. Patients who did not go through with the surgery due to contraindications, lack of response and who did not meet the criteria for discontinuation resumed ruxolitinib, paclitaxel, and carboplatin in less than 6 weeks after cycle 3. Maintenance therapy consisted of oral ruxolitinib twice daily within 3 weeks of completion of the sixth cycle. Phase I patients were followed until the adverse effects resolved.

In phase II, patients were randomly allocated to two groups with different arms of treatment. Arm 1 involved six cycles. The initial three cycles included paclitaxel IV on the first, eighth, and 15th day, and IV carboplatin on day 1, repeated for three cycles every 21 days, provided there are no unacceptable adverse effects or disease progression. Patients underwent TRS within 6 weeks after the third cycle. Cycles 4–6 followed a similar regimen and were commenced within 4 weeks of TRS. Treatment was repeated for three cycles every 21 days. Arm 2 patients received oral ruxolitinib, twice daily for the first 21 days, IV paclitaxel on the first, eighth, and 15th day, and IV carboplatin on day 1, repeated for three cycles every 21 days. Patients underwent TRS in less than 6 weeks of the third cycle. Commencement of cycles 4–6 after 4 weeks of TRS. Patients in phase II were followed quarterly for 2 years, then twice per year for 3 years.

In Phase I, 17 patients were enrolled. The maximum tolerated dose selected for both phases included 70 mg/m^2 for paclitaxel, 5 mg/m^2 for carboplatin, and 15 mg/m^2 for ruxolitinib. Phase II

involved 130 patients with a median follow-up of 24 months. Five grade 5 adverse events were recorded in phase II, with two in arm 1 and three in arm 2. These events were deemed unrelated to treatment, except for a febrile neutropenia incidence in arm 2. Furthermore, arm 2 experiences a tendency toward a higher incidence of grades 3–4 anemia, thromboembolic events, grades 3–4 neutropenia, and febrile neutropenia. The hazard ratio for PFS was calculated at 0.702, suggesting a potential benefit in arm 2. However, a *P*-value of .059 was calculated, indicating marginal statistical significance. Median PFS durations were 11.6 months in arm 1 and 14.6 months in arm 2. The hazard ratio for OS was 0.785, showing no significant difference between the arms ($P = .70$). Additionally, there were no notable disparities in the rates of total gross resection between the arms. This trial concluded that the utilization of ruxolitinib, in combination with paclitaxel and carboplatin was well-endured, with no significant toxicities, and successfully prolonged patients' PFS[14].

Between 2012 and 2019, the FDA approved four other JAK inhibitors: tofacitinib, baricitinib, fedratinib, and upadacitinib. Tofacitinib has pan-JAK inhibition activity but shows specificity to selective inhibition of JAK1 and JAK3. Baricitinib is a selective JAK1 and JAK2 inhibitor approved for rheumatoid arthritis treatment. Fedratinib, a selective JAK2 inhibitor, is approved for the treatment of MF, while upadacitinib, a JAK1 inhibitor, is approved for rheumatoid arthritis patients with no response or intolerance to methotrexate. In 2022, two new JAK inhibitors were approved by the FDA: abrocitinib, a JAK1 inhibitor with moderate JAK2 activity, approved for moderate-to-severe atopic dermatitis, and pacritinib, a JAK2 inhibitor, approved for MF treatment[8]. Preclinical data suggest a possible cytotoxic effect of fedratinib on OC cells[15]. However, there are no clinical trials available to support the impact of fedratinib or other JAK inhibitor in OC.

Despite advancements in treatment protocols, OC remains the most lethal gynecological cancer and a formidable challenge due to the resistance commonly encountered with current therapeutic options. Recent strides in understanding the biological microenvironment of OC have unveiled the pivotal role of the JAK/STAT pathway in tumorigenesis and drug resistance. This discovery has prompted the exploration of repurposing ruxolitinib, a JAK inhibitor, for treating this challenging disease. An overwhelming amount of preclinical and clinical data indicate that ruxolitinib exerts cytotoxic effects and can enhance the efficacy of standard chemotherapeutic agents. Repurposing ruxolitinib could significantly improve the lives of OC patients. It has already been shown to prolong PFS. However, addressing additional parameters such as quality of life, disease burden, and OS is crucial to comprehensively evaluate its impact. Further basic and clinical research is imperative to underscore the potential anticancer properties of ruxolitinib and, potentially, other JAK inhibitors.

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