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Synergistic lethal effect between PI3K/mTOR inhibitor Voxtalisib and arsenic trioxide on human leukemic KG-1 cell line

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Abstract: Myeloid/lymphoid neoplasms with FGFR1 rearrangement(also known as 8p11 myeloproliferative syndrome, EMS) is a distinct disease entity in the current WHO classification. These patients frequently (~80%) progress to acute myeloid leukemia (AML) and have a poor outcome with a 5-year survival rate of < 20%. To identify the potential treatment regimen on these patients, the four reagents (Idarubicin, arsenic trioxide, Voxtalisib and Ruxolitinib) were applied on KG-1 cells. Our results showed that the KG-1 cell line was resistant to idarubicin. However, the dual PI3K/mTOR inhibitor Voxtalisib, rather than JAK1/2 inhibitor Ruxolitinib could be effectively against KG-1 cells. Arsenic trioxide(As2O3) combined with Voxtalisib synergistically inhibitted the viability of KG-1 cells. We also found that the combination treatment more significantly reduced the colony formation, induced apoptosis, decreased Bcl-2 expression, but increased caspase-3 expression as compared to the single drug treatment. Additionally, As2O3 enhanced the effect of Voxtalisib which decreased the phosphorylation of PI3K, AKT and mTOR. These data suggests that Voxtalisib in combination with As2O3 may provide a novel and efficacious therapy regimen for patients with EMS.
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Key words: 8p11 myeloproliferative syndrome, Voxtalisib, Arsenic trioxide, KG-1 cells

1. Introduction

8p11 myeloproliferative syndrome (EMS) or stem cell leukemia/lymphoma syndrome (SCLL) is considered a rare entity with a high rate of progression to acute leukemia (AL), of which transformation occurs from 0 days to 24 months, with a mean time of 4.2 months (Jackson CC et al., 2010). Recently, EMS was reclassified by the World Health Organization (WHO) as 'myeloid/lymphoid neoplasm with FGFR1 rearrangement, highlighting the importance of the FGFR1 rearrangement'(Arber DA et al., 2016). Previous reports have shown that a molecular disruption of the FGFR1 gene results in a novel fusion gene and chimeric protein with constitutive activation of the FGFR1 tyrosine kinase and thereby promoting activation of downstream pathways, such as PI3K/AKT, STAT1/5, and phospholipase C (PLC)-γ(Chen J et al., 2004; Dong S et al., 2007). The receptor tyrosine kinase of FGFR1 is a good theoretical target for therapy with tyrosine kinase inhibitor (TKI). However, TKI alone is likely insufficient to produce indepth remissions in these patients (Khodadoust MS et al., 2016). It also seems that EMS patients are unresponsive to traditional chemotherapy. Therefore, hematopoietic stem cell transplantation (HSCT) remains the only hope for remission (Morishige S et al., 2016). Novel therapeutic strategies are urgently required to improve the currently unfavorable outcome of EMS patients.

The PI3K/AKT/mTOR signaling axis acts as a convergence point for a multitude of upstream signals and plays a pivotal role in cellular survival, tumor formation and growth(Vivanco I et al., 2002). The JAK/STAT plays a critical role in cellular processes involved in regulating tumor metabolism, proliferation, and chemoresistance (Dodington DW et al., 2018; Roberts KG et al., 2017). Therefore, the PI3K/AKT/mTOR and JAK/STAT pathways have been considered as theoretical targets. Arsenic trioxide (As2O3) is one of the earliest drugs used in the treatment of cancer in China. Due to the high efficacy and safety of As2O3 in treating acute promyelocytic leukemia (APL) and other malignant

solid tumors, As2O3 in combination treatment with other drugs was usually used for various malignant tumors (Takahashi S, 2010; Wang T et al., 2018). However, there are still few study about its effect on myeloid/lymphoid neoplasms with FGFR1 rearrangements.

The KG-1 cell line was obtained from a 59-year-old patient diagnosed with EMS that evolved into in acute myeloid leukemia (AML). The KG-1 cell line expressed an in-frame FGFR1OP2-FGFR1 fusion transcript, with the fusion of exon 4 of FGFR1OP2 to exon 9 of FGFR1, which could induce myeloid leukemia and T-Cell lymphoma in a mouse model. Therefore, The KG-1 cell line provides a unique model for studying EMS (Gu TL et al., 2006; Qin H et al., 2016).

In the present study, we aimed to offer a theoretical treatment regimen. The four reagents (Idarubicin, As2O3, Voxtalisib and Ruxolitinib) were applied on KG-1 cells, furthermore, their anti-cancer effects and synergy were evaluated and the underlying mechanism were explored.

2. Materials and methods

2.1 Cell line and cell culture

Human leukemic cell line KG-1 was purchased from ATCC (Manassas, USA). Cells were cultured in IMDM (Hyclone, Massachusetts, USA) supplemented with 20% fetal bovine serum (Gibco, Massachusetts, MA，USA) at 37°C in a 5% CO2 atmosphere.

2.2 Reagents and antibodies

DMSO(control) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Voxtalisib and Ruxolitinib was purchased from Selleckchem (Houston, USA), dissolved in DMSO and stored at −80°C until use. Idarubicin powder (Pfizer, USA) and As2O3 powder (Beijing Double-Crane Pharmaceutical Co., Ltd., Beijing, China) was dissolved in phosphate-buffered saline (PBS). β-actin antibody was bought from Santa Cruz Biotechnology (Texas, USA). Anti-AKT, anti-phosph-AKT, anti-PI3K, anti-phosph-PI3K, anti-mTOR, anti-phosph-mTOR, anti-Bcl-2 and anti-active caspase-3 were purchased from Abcam (Cambridge, UK). The HRP-conjugated goat anti-rabbit IgG and horse anti-mouse IgG secondary antibody were purchased from Jackson ImmunoResearch (Lancaster, USA).

2.3 Cell viability assay

Approximately 5,000 cells suspended in 100 μl medium were plated onto 96-well plates. Different concentrations of Ruxolitinib, Voxtalisib, Idarubicin and As2O3 alone or in combination were added to medium in 96-well plates and incubated for 48 h. 10μl CCK8 (Biosharp Technology Inc., China) was added to each well and incubated for another 1.5～3 h at 37°C. The absorbance at 450 nm was measured using a Multiskan FC spectrophotometer (Thermo Fisher, Massachusetts, USA).

2.4 Cell apoptosis and colony formation assay

The apoptosis assay was performed using an Annexin V-FITC /PI Staining Kit (BD Bioscience). KG-1 cells at a density of 5×10^5 cells were cultured for 48 h in 6-well plates in the presence of control solvent (DMSO), Voxtalisib, As2O3, the combination of Voxtalisib and As2O3. Induction of apoptosis was evaluated by flow cytometry using Annexin V/PI Staining Kit according to the manufacturer's protocol (BD Biosciences, San Jose, USA). Samples were acquired with BD FACSCanto System and data were analyzed with BD FACSDiVa software.

Colony formation assays was done in soft agar according to the manufactures' protocol (PMC4353381, doi: 10.3791/51998). The cell density was 10000/ plates and cells were incubated at 37℃ for 14 days. Routine colony were stained with crystal violet, and accumulation of 50 cells or more were scored as one colony. The experiment experiments were carried out.

2.5 Quantitative polymerase chain reaction(Q-PCR)

Total RNA was extracted using TRIzol reagent (Invitrogen, Massachusetts, USA) and the cDNA was obtained using Hieff™ First Strand cDNA Synthesis Kit (YEASEN, Shanghai, China). The mRNA level was detected in accordance with the

instructions of SYBR® Premix Ex Taq™ II(TliRNaseH Plus) Kit (TaKaRa, Otsu, Shiga, Japan). The results were reported as $2^{-\Delta\Delta CT}$ to calculate relative changes in the expression of apoptosis-related genes, each sample was detected in duplicate. The primer sequences were as follows: The primer sequences were as follows: Bcl 2, forward 5'-CAGGAAACGGCCCGGAT-3', reverse, 5'- CTGGGGCCTTTCATCCT CC-3'; Caspase-3, Foraward 5'-CTCTGGTTTTCGGTGGGTGT-3', Reverse 5'-TCCAGAGTCCATTGATTCGCT-3'; GAPDH, Forward 5'-GAAGGTGAAGGTC GGAGTC-3', Reverse 5'-GAAGATGGTGATGGGATTTC-3'.

2.6 Western blotting analysis

The operation was performed according to the whole protein extraction kit, and lysate was added. Equal amounts(40 μg) of total protein were loaded onto 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) separation gel, and then electrophoretically transferred onto polyvinylidene difluoride membranes (Bio-Rad, Richmond, CA). The membranes were blocked with 5% skimmed milk for about 1 h, followed by incubation with primary antibodies at 4°C overnight, and then

incubated with secondary antibodies for 1 h at room temperature. The immunoreactive bands were visualized with an enhanced chemiluminescence kit and captured on X-ray film.

2.7 Statistical analysis

Data are presented as the mean ± standard error of the mean. The Analysis of Variance (ANOVA) was used to make comparisons between groups. All statistical analyses were performed using the SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was considered to be present if the P <0.05. Drug synergy was determined by combination index (CI) methods derived from Chou-Talalay equations using the CalcuSyn software (Biosoft, Cambridge, United Kingdom), CI < 1 indicates synergy; CI = 1 indicates an additive effect; CI > 1 indicates antagonism.

3. Results

3.1 The effects of compounds on KG-1 cells

The inhibition of traditional chemotheraputic reagents (IDA, As2O3), JAK1/2 signaling pathway inhibitor (Ruxolitimib), and PI3K/mTOR pathway inhibitor (Voxtalisib) were identified using CCK8 assay. As a result, the IC50 values of IDA and Ruxolitimib were 120.7μg/mL and 344.025nM, respectively, which were far higher that treatment tolerance dosages. However, Voxtalisib and As2O3 showed significant proliferation inhibition at low concentration(IC50: 110.86nM and 20.9μg/mL, respectively). The cell growth inhibition curves were shown in figure 1.

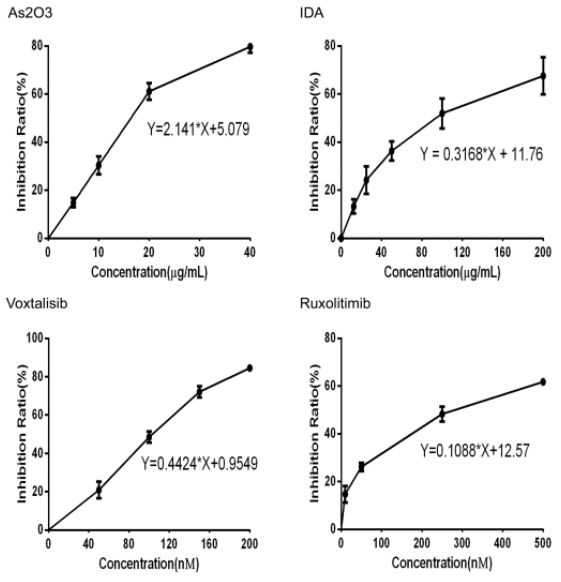

Figure 1: Cytotoxic effects of different reagents (As2O3, IDA, Voxtalisib and Ruxolitinib) on KG-1 cells.

3.2 Voxtalisib and As2O3 synergistically inhibited KG-1 cell proliferation

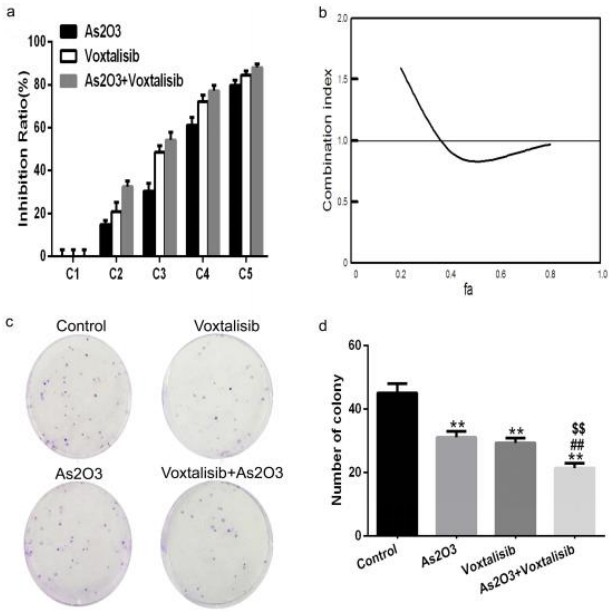

Figure 2 Effects of Voxtalisib and As2O3 alone or in combination in KG-1 cell viability.
(a) KG-1 cells were treated with different concentrations of Voxtalisib (0, 50, 100, 150, 200 nM as C1-C5) and/or As2O3 (0, 5, 10, 20, 40 μg/mL as C1-C5). (b) Combination index of Voxtalisib and As2O3. (c/d) Marked decrease in colony-forming capacity was observed. **, P < 0.01, vs control group; ##, P < 0.01, vs As2O3 group; $$, P < 0.01, vs voxtalisib group.

To examine whether As2O3 enhances the growth inhibition of KG-1 cells to Voxtalisib, we examined the KG-1 cell growth after the treatment with As2O3 in combination with Voxtalisib. The combination treatment of As2O3 and Voxtalisib substantially suppressed KG-1 cell growth as compared to As2O3 or Voxtalisib alone (Figure 2a). To explore whether the cell growth inhibition induced by the combination of As2O3 and Voxtalisib was additive or synergistic, we determined the combination index (CI) values according to the Chou-Talalay combination index equation. CI analysis revealed that the CI values ranged between 0.85 and 0.96 (Figure 2b). The results indicated that Voxtalisib and As2O3 synergistically inhibited KG-1 cell growth.

3.3 Combination of Voxtalisib and As2O3 significantly reduced the colony formation of KG-1 cells

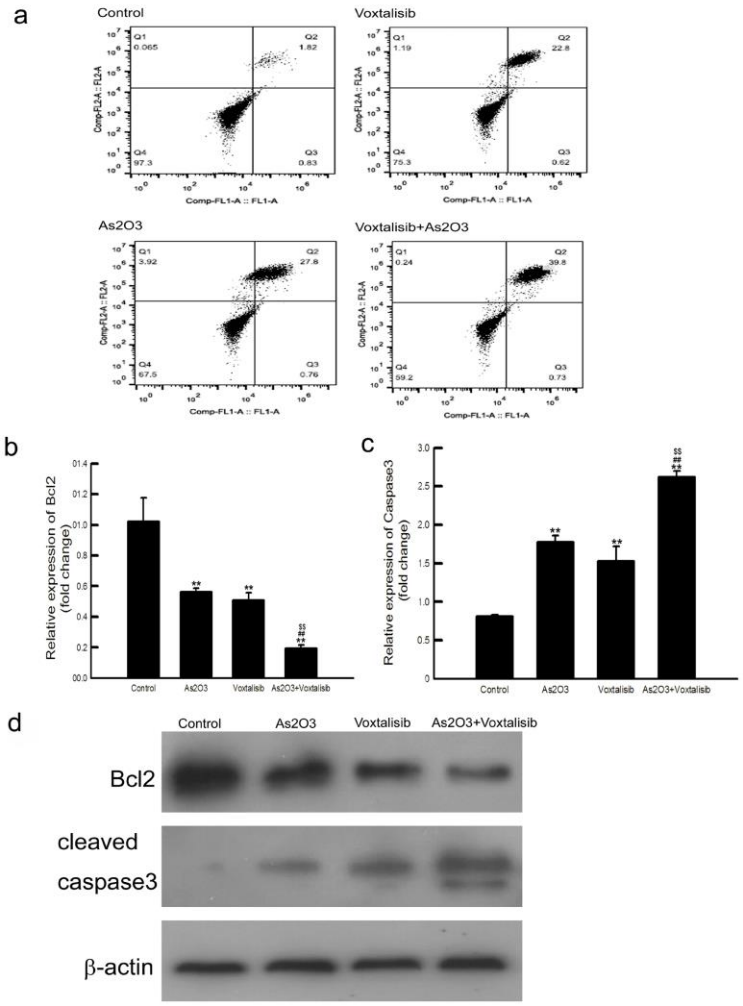

Figure 3 Apoptosis analysis and the expression of Bcl-2 and Caspase-3.(a)Apoptosis rate of KG-1 cells after treatment. The percentage of apoptotic cells (Annexin V positive) is indicated in Q2. Decrease in the mRNA expression of Bcl-2(b) & (c) increase in the mRNA expression of caspase-3. (d) Effect of As2O3 and Voxtalisib on protein expression levels of Bcl-2 and caspase-3 in KG-1 cells after a 48-h incubation.

Table 1：the number of KG-1 cell colonies formed on plates after treatment

Effects	Control	As2O3	Voxtalisib	Combination
Apoptosis rates	2.13± 0.315	30.7±3.2	29.2±6.3	42.5±2.75
Cloning counts	45.0±3.0	31.0±1.5	29.0±2.0	20.0±2.0

By comparing with control, the combination of 120nM Voxtalisib and 20μg/mL As2O3 or alone significantly inhibited the clonogenic activity of KG-1 cells. Additionally, the combination had substantially stronger inhibition of the clonogenic activity of KG-1 cells compared with Voxtalisib or As2O3 alone(Table 1).

3.4 Apoptosis increased after treatment with Voxtalisib plus As2O3 in KG-1cells

120nM Voxtalisib and 20μg/mL alone or in combination resulted in significant apoptosis of KG-1 cells as compared to the control,. The combination of Voxtalisib and As2O3 led to a marked increase in apoptosis compared with

Voxtalisib or As2O3 alone(Figure 3a).

3.5 The expression of apoptosis-related genes and proteins in KG-1 cells

To further investigate the underlying mechanism of apoptosis induced by Voxtalisib, As2O3, or Voxtalisib/As2O3 combination, the mRNA levels of apoptosis-associated genes caspase-3 and Bcl-2 were measured in KG-1 cells. Treatment with 120nM Voxtalisib and 20μg/mL alone led to significant decreases of Bcl-2 and increases of caspase-3 mRNA levels compared to control. The Voxtalisib/As2O3 combination dramatically decreased the expression of Bcl-2 and increased the expression of caspase-3 compared with the single drug treatment(P<0.01) (Figure 3b/c). In accordance with these results, western blot analysis confirmed the decreased expression of Bcl-2 protein along with elevated cleaved caspase-3 protein level after treatment with Voxtalisib and As2O3 (Figure.3d).

3.6 Voxtalisib and As2O3 inhibitted PI3K/AKT/mTOR signaling

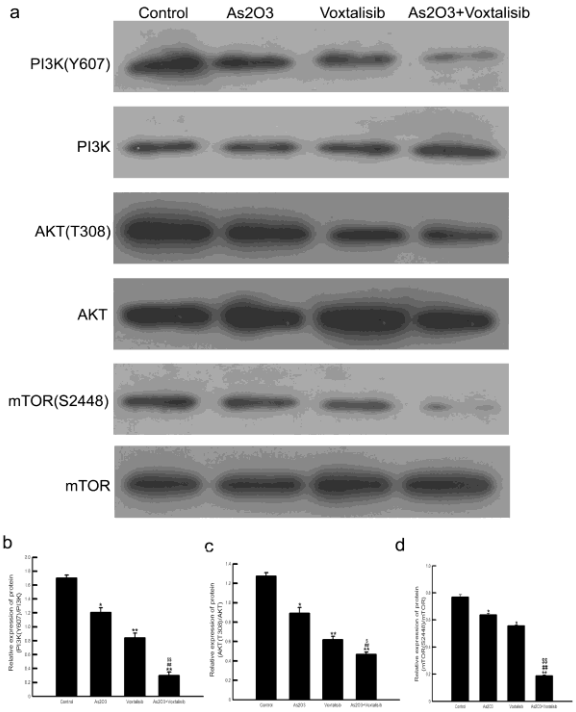

Figure 4 The phosphorylation of PI3K, AKT, and mTOR. (a/b) Western blot analysis of KG-1 cell lysates following treatment with Voxtalisib (120 nM) and As2O3 (20 μg/mL) for 48 h. p-PI3K, p-AKT, and p-mTOR levels were evaluated to assess the suppression of the PI3K/AKT/mTOR pathways by Voxtalisib and/or As2O3(protein expression levels were determined via densitometry). **, P < 0.01, vs control group; ##, P < 0.01, vs As2O3 group; $$, P < 0.01, vs Voxtalisib group.

The results of western blotting displayed that 20μg/mL As2O3 enhanced the effect of 120nM Voxtalisib which decreased the phosphorylation of PI3K, AKT and mTOR. The Voxtalisib/As2O3 combination markedly down-regulated p-PI3K, p-AKT and p-mTOR expression compared with Voxtalisib or As2O3 alone (Figure. 4).

4. Discussion

Chemotherapy resistance is a life-threatening problem in EMS patients. In the present study, we demonstrate that KG-1 cells are highly refractory to traditional chemotherapy drug, IDA. However, inhibition of the PI3K/AKT/mTOR, rather than the JAK/STAT pathway, effectively induces apoptosis, and As2O3 can reinforce the cytocidal effect of PI3K/AKT/mTOR pathway inhibitor against KG-1 cells.

It has been reported that the PI3K/AKT/mTOR signaling pathway may mediate anti-apoptotic activities by changing the ratio of pro- and anti-apoptotic proteins(Choi EJ et al., 2014). However, its efficacy in the treatment of EMS and the underlying antitumor mechanism has not been elucidated yet. This is the first study to show that the dual PI3K/mTOR inhibitor Voxtalisib can significantly inhibit proliferation of KG-1 cells and induce its apoptosis. The anti-proliferative effect of Voxtalisib was further assessed by colony-forming assay. We found that colony numbers were reduced in KG-1 cells treated with Voxtalisib. Voxtalisib (SAR245409, XL765, S7646), a novel pan-PI3K/mTOR inhibitor, is being evaluated as anti-leukemia and anti-lymphoma therapies(Zhang L et al., 2018; Papadopoulos KP et al., 2015; Thijssen R et al., 2016). An initial human phase-I Voxtalisib clinical study has demonstrated favorable toxicity, tolerability profiles, and better anti- relapsed or refractory lymphoma effects(Papadopoulos KP et al., 2015). Our study indicates that the dual PI3K/mTOR inhibitor Voxtalisib blocks proliferation which is in agreement with previous findings of primary chronic lymphocytic leukemia cells(Thijssen R et al., 2016).

Previous studies have been performed to investigate the interactions of As2O3 combined with other drugs, because combination treatment may decrease single drug administration and simultaneously enhance the clinical therapeutic benefit. It has also been noticed that As2O3 reduce the activation of the AKT/mTOR pathway by reducing AKT, p70S6K and rpS6 phosphorylation in human leukemia cells(Yu Y et al., 2014; Calviño E et al., 2011). However, whether the combination of As2O3 with the dual PI3K/mTOR inhibitor

Voxtalisib induces synergistic effect to trigger apoptosis in KG-1 cells has not yet been studied. Our results revealed that the combination treatment of Voxtalisib and As2O3 synergistically inhibited KG-1 cell growth as evidenced by analysis of the combination index (CI) values < 1. We found that Voxtalisib alone was capable of inducing a modest cell apoptosis and reducing the colony formation, As2O3 could significantly enhance these two effects. Wang T et al. also identified a synergistic anti-leukaemia effect of As2O3 and TKI in Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) and chronic myelogenous leukaemia (CML)(Xia Y et al., 2013; Wang T et al., 2018). Notably, in this context, the apoptosis-promoting effects of As2O3 were identified as the most remarkable effects within the anti-tumour activities of this molecule(Wang T et al., 2018).

It is well known that apoptosis is an important cause of cytotoxicity. The effectiveness of As2O3 in combating a hematological tumor is mainly due to the regulation of apoptosis-related proteins, including the down-regulation of Bcl-2 and the activation of caspases(Alamolhodaei NS et al., 2015). Therefore, our focus in this study was on apoptosis induced by As2O3 and Voxtalisib. In the present study, we demonstrated that As2O3 induced the apoptosis of KG-1 cells, further analyses revealed that obvious changes in the expression of anti-apoptotic protein Bcl-2 and pro-apoptotic protein caspase-3 were observed after treatment with As2O3 by Western blot analysis, and the anti-apoptotic proteins AKT, p-AKT, mTOR as well as phosphorylated mTOR (p-mTOR) were also downregulated, which were in agreement with previous findings of the As2O3-triggered apoptosis of lung cancer cells and SGC-7901 cells(Yu Y et al., 2014). Additionally, the combination treatment of As2O3/Voxtalisib markedly down-regulated p-PI3K, p-AKT and p-mTOR expression and dysregulated the expressions of Bcl-2 and caspase-3 proteins compared with the single compound treatment.

Taken together, we provide evidence that the human leukemic KG-1 cell line which is resistant to anthracycline anticancer drug, idarubicin(IDA). However, the dual PI3K/mTOR inhibitor Voxtalisib, rather than JAK1/2 inhibitor Ruxolitinib, can be effectively against KG-1 cells. Arsenic trioxide(As2O3) combined with Voxtalisib exerts a synergistic effect on inhibiting the viability of KG-1 cells. The combination treatment more significantly reduces the colony formation, induces apoptosis, decreases Bcl-2 expression but increases caspase-3 expression than the single drug treatment. Additionally, As2O3 can enhance the effect of Voxtalisib which decreases the phosphorylation of PI3K, AKT and mTOR. The underlying mechanism involves apoptosis-related genes and PI3K/AKT/mTOR pathway. These results of the current study suggest that combined administration of Voxtalisib and As2O3 should be considered as a promising therapeutic tactic for EMS patients.

Conflict of interest statement

None of the authors of this paper has a financial or personalrelationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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