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Review Article

Prospect of research and clinical application of arsenic compounds in chemotherapy for gynecological malignant tumors

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ABSTRACT

Arsenic compounds, including various arsenic-containing compounds such as intravenous use of arsenic trioxide (ATO) and an oral tetra-arsenic tetra-sulfide (As4S4) -containing formula named the Realgar-Indigo naturalis formula (RIF). RIF, also known as Compound Huangdai Tablets, which exert anti-tumor effects through a variety of mechanisms, such as the induction of programmed cell death, induction of G1 or G2/M phase arrest, epigenetic regulation of miRNAs, and suppression of cancer stem cell properties. International multicenter clinical studies have shown that ATO and RIF have anti-tumorigenic effects on hematological tumors and some solids. Arsenic compounds also been used in the treatment of cervical cancer, endometrial cancer, ovarian cancer, especially advanced drug-resistant ovarian cancer. This article introduces the progress of ATO in combination chemotherapy, such as ATO with paclitaxel, adriamycin, cisplatin, etc in solid tumors and gynecological malignant tumors. The side effects associated with arsenic treatment, including cardiac disorders, skin and bone marrow suppression, etc. are also discussed in this review. Oral arsenic drugs also have a good therapeutic effect, it may be an outpatient oral chemotherapy new model for RIF to treatment recurrent ovarian cancer.

1. Background

Chemoresistance limits the clinical application of chemotherapy and significantly affects the patient's prognosis. Although the National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend a second-line, single chemotherapy drug for advanced drug-resistant ovarian cancers. Drugs that meet these criteria include paclitaxel, liposomal doxorubicin, oxaliplatin, etc., however, the treatment success rate is only 20%. New targeted drugs and immunosuppressive drugs have been developed for clinical application, however, when taken by patients with drug-resistant gynecological tumors, their efficacy rates are still very low. Therefore, the study of new chemotherapy drugs and chemotherapy regimens remains an ongoing challenge for gynecological oncologists.

Chemical medicines containing arsenic include realgar, orpiment, white arsenic, and so on. Currently, clinical uses of arsenic agents include intravenous use of ATO and oral arsenic formulations RIF.

In support of the anti-tumor mechanisms of arsenic, including anti-apoptosis, inhibition of blood vessel growth, etc., multicenter clinical studies have shown that arsenic has anti-tumorigenic effects on hematological tumors, such as acute promyelocytic leukemia (APL).[1] Arsenic also has some anti-cancer effects on solid cancer cells, such as hepatocarcinoma, bone tumors, colon cancer, lung cancer, and others.[2–5] Oral arsenic drugs not only have a good therapeutic effect, but also change the mode of chemotherapy from inpatient to outpatient. Outpatient chemotherapy treatments improve patients' quality of life. While arsenic has attracted the attention of malignant oncologists, few reports on the use of arsenic in treating gynecologic malignant tumors have been mentioned, especially in advanced drug-resistant cervical cancer, endometrial cancer, and ovarian cancer. Therefore, to improve the current state of the literature, the basic research, clinical application status, and future application model of gynecological malignant tumor drugs are summarized in this review.

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2. Pharmacokinetic and pharmacological properties, and anti-cancer mechanism of arsenic compounds

Arsenic is a non-metallic element that has been considered a poison for more than 2000 years. It has several forms that can be found in organisms, such as inorganic arsenic, organic small molecules arsenic, arsenic organic compounds, and biological macromolecules containing arsenic. Arsenic compounds have significantly differing biological effects and their pharmacokinetics are different *in vivo* and *in vitro*.

Inorganic arsenic undergoes oxidative methylation and reduction processes in the body, resulting in the production of various methylated arsenic metabolites that are ultimately excreted. Trivalent arsenic can bind to a variety of important sulfhydryl enzymes, resulting in inactivation of these enzymes, which affects normal cell metabolism and causes cell damage.[6] Pentavalent arsenic can compete with phosphoric acid to break down and inhibit the high-energy phosphate bond.[7] This disrupts adenosine triphosphate (ATP) production, impacting energy metabolism and so on.[8] Several studies had shown that ATO can inhibit tumor growth and promotes the apoptosis of various solid tumors *in vitro*.[9,10] Arsenic-containing Chinese medicines have been used therapeutically since ancient times. In the 1970s, intravenous ATO was used for the treatment of APL and other cancers, and was considered the best treatment at the time.[11] In response to the success of arsenic-containing therapeutics, the US Food and Drug Administration (FDA) approved the combined use of all-trans retinoic acid trioxide (ATRA) for the treatment of APL in 1995.[12] However, there are few reports on the use of ATO in the clinical treatment of solid tumors.

Another oral preparation containing arsenic is known as RIF, or Compound Huangdai Tablets. Each RIF tablet weights 270 mg, including Realgar 30 mg, indigo naturalis 125 mg, Danshen 50 mg, Taizishen 45 mg, coating 20 mg. The main ingredients present in the 30 mg of Realgar is AS_2S_2. Experimental studies by Wang L et al.[13] summarized the anti-APL activity of RIF *in vivo* and *in vitro*. Briefly, their results show that indigo naturalis and Salvia miltiorrhiza promote intracellular arsenic transport by regulating the expression of water glycerophospholipid protein. Various components had an obvious synergistic effect on the differentiation and apoptosis of APL cells.[14,15]

3. Advances in research and potential clinical applications of arsenic in the treatment of hematological tumors and solid tumors

3.1. Progress in the use of ATO in hematological tumors

At present, the research and clinical application of anti-hematologic agents include intravenous ATO and oral Compound Huangdai tablets. The molecular mechanism of ATO in the treatment of anti-hematologic tumors was primarily through promoting the cleavage of the oncogenic fusion protein promyelocytic leukemia/retinoic acid receptor-α (PML/RARα), which results in apoptosis, and to regulate the expression of genes and proteins. Sulfhydryl is an important chemical in arsenic-induced apoptotic pathways, such as family-dependent cysteine protease-dependent apoptotic pathway and the mitochondrial apoptosis pathway.[2,8–10]

Zhu et al. reported a multicenter clinical study in which they explored the use of oral Compound Huangdai tablets to treat APL. In 2009. They treated 5000 Chinese APL patients with oral RIF therapy.[14] They found that the clinical efficacy of this oral arsenic preparation was similar to that of the intravenous preparation, and the safety was higher and associated with both improved quality of life and reduced medical cost. These results indicate that the outpatient treatment mode of low and high-risk APL patients in China should be integrated into clinical practice. Advances in the treatment of APL by oral arsenic-containing medication RIF how that RIF assisted particularly in the resolution of complications associated with induction therapy. Another randomized, multicenter phase III clinical trial was conducted investigating RIF, and intravenous ATO as a treatment for APL.[15] In this study, 242 patients with APL were randomized to either oral RIF (60 mg/kg) or oral RIF (0.16 mg/kg) in combination with ATRA (25 mg/m^2). After achieving complete remission (CR), all patients received 3 cycles of consolidation chemotherapy and maintenance therapy, first ATRA and then RIF or ATO treatment for 2 years. Results displayed that there was no significant difference in CR percentage between the RIF group and the ATO group (99.1% vs. 97.2%, $P > 0.05$) and there was also no different between the RIF group and the ATO group when they looked at overall 3-year survival rate (99.1% vs. 96, 6%, $P > 0.05$). The incidence of adverse reactions was similar in both groups. These results show that the use of oral RIF + ATRA as a first-line treatment for APL was not inferior to intravenous ATO combined ATRA, indicated it could be used as a routine treatment option in some patients.

3.2. Progress in the use of ATO in solid tumors

ATO has been proven to be effective not only in the treatment of chronic lymphocytic leukemia and acute myeloid leukemia, but also for some solid tumors, such as hepatocellular carcinoma, head and neck cancers, lung cancer, stomach cancer, and so on. ATO could also cause common side effects.[14–17] ATO chemoembolization or combination chemotherapy for advanced hepatocellular carcinoma cells (HCC) could significantly improve the effectiveness of chemotherapy and patient's prognosis.[18] For example, ATO combined with *cis*-diamminedichloroplatinum (CDDP) could reduce the proliferation rate of HCC, increase the apoptosis rate of cancer cells, and increase the sensitivity of CDDP to chemotherapy. These results indicate that ATO provides a foundation for overcoming HCC resistance in CDDP patients and improves the effectiveness of CDDP chemotherapy.[17] Other studies have shown that a low dose of CDDP could also induce cancer cell autophagy via the adenosine monophosphate-activated protein kinase-signal transducer and activator of transcription 3 (AMPK/STAT3) signaling pathway in head and neck cancers. Low-dose ATO and CDDP combination treatment protocol can also induce cell death and exacerbate autophagy in head and neck cancer-initiating cells (HN–CIC) via the AMPK-STAT3 pathway. High-dose combination therapy using ATO and CDDP was shown to exerts a synergistic apoptotic effect on a large number of solid tumor cell lines. It is worth noting, though, that these treatments could have significant side effects in patients.[19]

The study of ATO in combination with cisplatin also shows a synergistic effect on non-small cell lung cancer. ATO was thought to have anticancer activity in cisplatin-resistant non-small cell lung cancer cells (NSCLC) PC-9/CDDP and PC-14/CDDP. The effect of ATO on cisplatin-sensitive NSCLC PC-9 and PC-14 cell lines was also evaluated. It is worth mentioning that the biochemical half maximal inhibitory concentration (IC50) of cisplatin-resistant PC-9/CDDP and PC-14/CDDP cells was significantly lower than that of cisplatin-sensitive PC-9 and PC-14 stem cells. Decreased regulation of the glutathione S-conjugate (GS-X) pumping system may affected the accumulation of arsenic in the PC-9 cell line.[1]

4. Advances in ATO and oral arsenic research and clinical application of gynecological tumors

Among gynecological malignancies, ATO was first used in the local treatment of cervical cancer. As research progressed, it was also used to treat other gynecological malignancies. Experimental studies have shown that arsenic agents promote cell apoptosis and increase the sensitivity of gynecological malignant tumor cells to radiotherapy and chemotherapy, increasing the overall effectiveness of these therapeutics in patients with drug resistance and recurrence.

4.1. Progression in developing ATO use in the treatment of cervical cancer

The studies showed that ATO had an inhibitory effect on the growth

of cervical cancer cells. Wen et al. conducted a study on the effects of ATO on HPV-positive cervical cancer cell lines HeLa and CasKi, and HPV-negative cervical cancer cell line C33A. Their results showed that after 1–10 μmol/L ATO treatment, the viability of C33A cells was reduced by 16%, and the viability of HeLa and CaSki cells was reduced by 48% ~60%, indicating that ATO had a stronger inhibitory effect on HPV-positive cervical cancer cells.[15] However, Wang et al. also showed that, compared with HPV-positive cervical cancer cells, HPV-negative cervical cancer cell line C33A was more sensitive in the medium containing ATO, and HPV18-positive cervical cancer cell lines HeLa and C4–I were more sensitive than HPV16-positive Caski and Siha cells.[20]

An *in vitro* study of Kang et al. using ionizing radiation combined with ATO found that the combined application of the two treatments could increase the sensitivity of cervical cancer cells to radiotherapy, and the sensitization mechanism may be associated with the combined activation of C-Jun N-terminal kinase (JNK)/MAPK and P38/MAPK (mitogen-activated protein kinase).

Signaling pathways to promote bcl-2 phosphorylation, change mitochondrial permeability, and then lead to cell cycle arrest and promote apoptosis of cervical cancer cells.[21] Yu et al. further used ATO *in vivo* and *in vitro* to confirm the radio-sensitization effect of ATO, and the results showed that the radio-sensitization effect of ATO was equivalent to that of CDDP, but the side effects were reduced and safer than CDDP.[22]

Both *in vitro* study and animal experimental studies show that ATO had a radio-sensitization effect. These studies provide a new treatment method for cervical cancer patients who are insensitive to radiotherapy. The mechanism of action for ATO on cervical cancer may affect cell proliferation, apoptosis, and invasion after the treatment of hypoxia-inducible factor-1α (HIF-1α), and the effect was related to time and dose.[23] In addition, how to use ATO to improve the efficacy of high-risk HPV-related cancers has become a concern.[20]

4.2. Progress in the application of ATO for the treatment of endometrial cancer

In recent years, adjuvant chemotherapy and endocrine therapy are important adjuvant treatments after surgery for endometrial cancer. It is urgent to find more effective and less side effect-inducing drugs to give to patients with chemotherapy resistance or progesterone resistance. This study shows that ATO used in endometrial cancer research was more effective on endometrial cancer cells and had less side effects, indicating progress has been made.

Wang et al. studies found that ATO acts on endometrial cancer HEC-1A cells, and could significantly inhibited the growth of HEC-1A cells better than CDDP. This suggests that ATO had potential application value in the treatment of endometrial cancer. Further studies found that ATO inhibited the proliferation of endometrial cancer cells and promoted apoptosis in a dose- and time-dependent manner, in which human telomerase reverse transcriptase (hTERT) might work.[24] Bae-Jump and other studies have shown that ATO could inhibit the expression of mRNA and protein of estrogen receptor in endometrial cancer cells through the MAPK pathway, and exerted its anti-tumor effect. Further studies have shown that ATRA could have a synergistic effect in combination with ATO, and could synergistically inhibit the growth of endometrial cancer HEC-2B cells, its effect was time- and dose-dependent. Animal studies have shown that intraperitoneal injection of ATO could significantly inhibit the growth of human transplanted tumors of endometrial cancer in nude mice. Compared with CDDP, the inhibitory effect was stronger and the adverse reactions were weaker. The mechanism of action was related to the upregulation of proapoptotic counterpar Bax and downregulation of the antiapoptotic protein Bcl-2 protein expression by ATO, to induce cell apoptosis and downregulation of the protein expression of E-type cyclin (Cyclin-E), cyclin-dependent kinase 2 (CDK2), and nuclear protein Ki-67, to cause cell cycle arrest and decrease the expression of estrogen receptors in transplanted tumors.[25]

Sugiura et al. reported the first case of both APL and endometrial cancer occurring in the same patient. The patient was treated with ATO and consolidation therapy, followed by gynecological surgery and 15 weeks of paclitaxel and carboplatin regimen to treat endometrial cancer, and there was no recurrence in at 7 years after treatment. In this case, ATO consolidation therapy may be better because of its decreased blood toxicity.[26] Furthermore, our center reported a case of using ATO to treat platinum-resistant endometrial cancer patients, the results showed that platinum-resistant patients had better disease control and long-term survival with ATO treatment.[27]

Although there were few reports of ATO use in the treatment of endometrial cancer and relapsed drug resistance patients, the above results indicate that ATO is a promising new drug for the treatment of platinum and progesterone resistant cancers, as well as providing an experimental basis for the clinical treatment of platinum and endocrine resistance.[28]

4.3. Progress in the application of ATO in treating ovarian cancer

Chemotherapy is an important adjuvant treatment for ovarian cancer, but once drug resistance occurs after chemotherapy, the prognosis is poor. Therefore, finding effective drugs for patients with recurrent and metastatic ovarian cancer and chemotherapy-resistance is of great significance for improving the survival of patients with ovarian malignant tumors.

The study of ATO in the treatment of ovarian cancer was mainly focused on the anti-tumor effects of inhibition of abdominal metastasis, combined medication, and effects on drug-resistant cells. The study of Hannah M et al. showed that the main mechanism of ATO against ovarian cancer was related to inducing apoptosis of ovarian cancer cells.[29] Other mechanisms may be related to the activation of caspase and poly ADP-ribose polymerase (PAPR) in the apoptotic pathway and down-regulation of the expression of p-AKT protein, which induces SKOV3 cells to undergo apoptosis.[30] Zhang et al.'s results show that ATO can significantly inhibit the proliferation of human ovarian cancer cell line SKOV3. ATO inhibits the proliferation of ovarian cancer cell line COC1 in a concentration- and time-dependent manner, and can be combined with CDDP for a synergistic effect. ATO can inhibit abdominal cavity metastasis of ovarian cancer, thereby prolonging the survival time of patients. ATO inhibits the peritoneal infiltration activity of ovarian cancer cells *in vivo* and *in vitro* in a dose-dependent manner. The mechanism may be related to the reduction of cell viability, inhibition of tumor cells attachment to peritoneal mesothelial cells, enhancing the interaction between tumor cells, downregulating the levels of matrix metalloproteinase (MMP) 2 and MMP-9, and upregulating the expression of MMP inhibitor (TIMP).[31]

Drug resistance is a major problem in the treatment of ovarian cancer.[32] The study has shown that ATO has an inhibitory effect on drug-resistant and non-resistant ovarian cancer cell lines. This study provides hope for patients with chemotherapy-resistant ovarian cancer. ATO was shown to have a growth inhibitory effect on cisplatin-resistant ovarian cancer cell line COC1/DDP. The mechanism was related to ATO's ability to upregulate tumor suppressor genes (Bax, p53, etc.) and downregulate the expression of lung resistance protein (LRP). Animal experiments have shown that ATO has a significant inhibitory effect on cisplatin-resistant ovarian cancer cell lines transplanted into the abdominal cavity of nude mice.[33] The mechanism was related to the positive and negative regulation of Fas and nm23H1 genes and N-myc and MTA1 genes, respectively. These results suggest that ATO has an inhibitory effect on drug-resistant ovarian cancer cells, making it a potential option in the treatment of drug-resistant ovarian cancer.

In clinic, how to successfully treat drug resistance is a major challenge facing gynecological oncologist. Di et al. reported a combined drug regimen using ATO and CDDP to increase the potential for successful treatment of ovarian cancer.[34] Their results show that the anti-proliferation and pro-apoptosis effects induced by ATO were closely related to 34 genes (23 upregulated genes and 11 downregulated genes).

The above results suggest that ATO combined with CDDP has therapeutic potential in the treatment of ovarian cancer, and is worthy of further preclinical and clinical research. At present, our center uses ATO-paclitaxel sequential chemotherapy to treat platinum-resistant ovarian cancer, and preliminary results show a good effect.

Although there were few reports on the use of ATO to treat patients with recurrent ovarian cancer and platinum resistance, the above results show that the application of ATO is expected to provide an experimental basis for the treatment of recurrent ovarian cancer and platinum resistance, and to provide new drugs for the clinical treatment of platinum resistance.

4.4. Research progress of oral arsenic in gynecological malignancy

Oral arsenic, has been showed to be a first-line treatment for APL in multi-center clinical studies. Five-year survival rates in these studies were more than 90%, with improved patient prognosis and quality of life, and greatly reduced hospitalization costs.[35] At present, there are few reports on the use of RIF in the treatment of gynecological malignancies. In our center, there were cases reported in ovarian cancer which are waiting for submission.

5. Advances of ATO in the combined chemotherapy

Although ATO has been shown to be effective as a single agent in the treatment of APL, it could not give satisfactory results in the treatment of various solid tumors. Recent research shows that ATO targets prolyl isomerase (Pin1), a master regulator of oncogenic signaling networks, at clinically relevant safe doses, inactivate a variety of oncoproteins, activate many tumor suppressors and global microRNAs, and inhibit the growth of triple-negative breast cancer tumors.[36] These results indicate that synergistic targeting of Pin1 by ATO and ATRA offers an attractive approach to combating breast and other cancers. ATO and other chemotherapy drugs, like CDDP, Paclitaxel, Doxorubicin, etc., have made great strides in the combined treatment of blood and some solid tumors. Vitamin C has a good sensitizing effect on ATO in a certain concentration range, which could reduce the dose of ATO and, at the same time, improve the effectiveness of the drug, reduce toxicity, and side effects.[37,38]

The combination chemotherapy protocols of ATO and chemotherapeutic agents had a synergistic effect on drug-sensitive and drug-resistant ovarian cancer cells. Zhang et al. used a combination index (CI) analysis to show that ATO and CDDP had a synergistic effect on improving antiproliferative and pro-apoptotic effects on ovarian cancer cells and cisplatin-resistant cancer cells.[34] The study by Byun et al. had shown that ATO and As_4O_6 could inhibit the growth of paclitaxel-sensitive and drug-resistant ovarian cancer cell lines by causing apoptosis[9]

5.1. The protocols of ATO combined with CDDP

ATO had a regulatory effect on the sensitivity of HCC to CDDP chemotherapy. Studies showed that ATO, when combined with CDDP therapy, could increase the sensitivity of HCC cells to CDDP chemotherapy by reducing the rate of HCC cell proliferation, promoting apoptosis, and increasing CDDP mortality in HCC cells. This provides a new therapeutic strategy for the treatment of drug resistant HCC cells by reducing HCC chemotherapy and improving the prognosis of HCC patients.[31]

5.2. The protocols of ATO combined with paclitaxel

ATO combined with paclitaxel have been shown to have a synergistic inhibitory effect on human colon cancer cell line CT26,[39] human myeloma cells,[40] and lung adenocarcinoma M5G80 cells *in vitro*.[41] For gastric cancer cell line MGC803, the rate of inhibition gradually increased with the prolongation of ATO treatment combined with paclitaxel, the effectiveness of treatment could be increased and the onset of drug resistance delayed *in vitro*.[42]

5.3. The combination protocols of ATO and Adriamycin

Studies using immunocytochemistry and the real-time reverse transcription polymerase chain reaction (RT-PCR) have shown that the combination of ATO and Adriamycin could synergistically induce apoptosis of adriamycin-selected drug-resistant leukemia K562 cells.[43]

5.4. The protocols of ATO combined with 5-fluorouracil (5-FU) regimen

Studies had shown that the combination of ATO and 5-FU could enhance the effects of apoptosis in cancer cells, regulate the expression of apoptosis-related genes (Bcl-2, Bax, Fas and FasL), and resist colon cancer in nude mice.[44] It had a significant inhibitory effect, which shows that the combination protocol had no obvious toxicity to the liver, kidneys, or hematopoietic system of nude mice bearing tumors.

5.5. The combination of ATO and anti-vascular regimen

Haghi A et al. studies have shown that *in vitro* combination of arsenic and anti-vascular drugs not only significantly inhibit the growth of cervical cancer HeLa cells, but also induce the apoptosis of cervical cancer cells and inhibit vascular endothelial growth factor. The expression of VEGF could block the growth of new blood vessels and further inhibit the proliferation and metastasis of cervical cancer cells, and this inhibitory effect was time- and concentration-dependent.[45]

6. Side effects of ATO

Previous studies have shown that ATO has a variety of anti-cancer mechanisms. This includes promoting the differentiation of tumor cells, inhibiting the growth of tumor cells, and inducing apoptosis.[36–40] ATO has a good anti-tumor effect but it is worth noting that ATO use can result in side effects, including gastrointestinal disorders, cough, fatigue, skin rash, bone marrow suppression, and so on. More serious side effects include hepatic failure and cardiotoxicity.[45–49]

At present, the anti-cancer mechanisms of ATO have been well studied in various solid tumors, such as HCC, colorectal cancer (CRC), breast cancer, and glioma, however only in the treatment of APL is the best effect seen. There are few reports in other malignant tumors. Compared with hematological malignancies, high-dose ATO is clinically needed for the anti-cancer activity of solid tumors.[50] Researchers are mostly carrying out combined treatment programs, and it has been reported that ATO could improve the efficacy of cisplatin in the treatment of oral cancer and ovarian cancer.[7,51] However, taking ATO in high doses could cause serious side effects to the heart and blood vessels. The main complications include differentiation syndrome and prolonged the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. Therefore, side effects should be handled in accordance with the recommended procedure.[52] Most patients tolerate ATO well. When using the recommended dose of 0.15 mg/(kg × d), only minor toxic effects were observed.[53]

7. Conclusion

In summary, the clinical application of arsenic compounds includes intravenous ATO and oral arsenic known as RIF. Basic research and clinical multi-center studies had proven their mechanism and efficacy. Due to the unique anti-tumor mechanism of ATO, which has been used in hematological tumors such as APL, chronic myeloid leukemia et al., also in some solid tumors including primary hepatocarcinoma, breast cancer, and bone tumors. ATO has inhibitory effects on gynecological malignancies including cervical cancer, endometrial cancer, and ovarian cancer, especially in the treatment of drug-resistant ovarian cancer tumors.

RIF are comparable to the intravenous preparation, and has been shown to be safer. RIF could improve the patient's quality of life, and reduce the patient's medical expenses.[54] Therefore, it is expected to be used as an outpatient oral chemotherapy for ovarian cancer and become a new treatment model for recurrent ovarian cancer based on "out-patient-oral-platinum-free model.

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Declaration of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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