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**LETTER TO THE EDITOR**

# Temporary effect of arsenic trioxide treatment of refractory extragonadal germ cell cancer

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## To the Editor

Relapsing, chemotherapy refractory, non-seminomatous germ cell cancer has a poor prognosis due to the limited treatment options. Surgery and radiotherapy can be used to reduce tumor burden as much as possible but when these treatment modalities are exhausted nothing is left but experimental treatment. Arsenic trioxide (ATO) has induced apoptosis *in vitro*, in several different solid tumors such as breast [1], prostate [2] and neuroblastoma [3]. Clinically, ATO has been proven effective in the treatment of patients with acute promyelocytic leukemia and multiple myeloma, as reviewed by Douer and Tallman [4]. Recently, SWOG reported the results from a phase II trial "Arsenic Trioxide in Treating Men With Germ Cell Cancer" (SWOG S0207). In summary, none of 20 patients responded to ATO but three adverse advents with death related to the treatment were reported [5]. Here, we report a clear biochemical and clinical response to ATO within a patient with a progressive and chemotherapy-resistant germ cell cancer disease.

In 1986 a male born 1959 was diagnosed with embryonal midline carcinoma with tumor both in the retroperitoneal lymph nodes and the mediastinum. At diagnosis both AFP (alphafetoprotein) and total hCG (human chorionic gonadotropin) were elevated; AFP was 55 (normal range $< 10$ μg/l) and total hCG was 51 500 (normal range $<10$ IU/l). Initially, the patient received four courses of cisplatin, vinblastine and bleomycin (CVB) followed by a retroperitoneal lymph node dissection. In the tumor specimens, viable cancer cells were microscopically detected and the patient received two courses of vinblastin, ifosfamide and cisplatin (VIP) as adjuvant treatment. In 1999 he relapsed with cytologically verified lung metastases and β-hCG was slightly elevated but not AFP. He then received two courses of chemotherapy with etoposide and cisplatin. Due to poor response, he then received one course of cisplatin, etoposide and ifosfamide followed by bilateral resection of the lung metastases. The tumor specimens demonstrated necrotic parts with remaining vital malignant tumor cells. In October 1999 consolidating high-dose chemotherapy with autologous peripheral blood stem cell support was given but in 2000 a new relapse appeared in the lung. In that situation a palliative intended treatment was initiated using paclitaxel and gemcitabine. Unfortunately, no effect was seen on β-hCG and the disease continued to progress slowly, also radiographically. In 2001 stereotactic radiotherapy was used to irradiate three lung metastases which led to local remission. During the summer of 2002 treatment with oral etoposide and methylprednisone was used but β-hCG continued to increase and a disturbing cough developed as the metastases progressed. In August 2002, ATO was given intravenously day 1–5 at a daily dose of 0.25 mg/kg BW /day and the cycle was repeated every fourth week. After two weeks the patient experienced a relief of the cough and β-hCG dramatically decreased (Figure 1). However, the symptoms started again after 9 weeks, accompanied by an increase in β-hCG. In October 2002 computed

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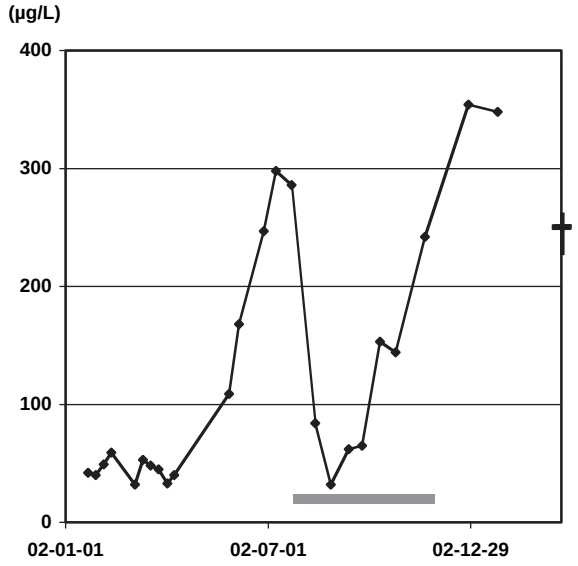


Figure 1. The levels of Beta hCG during time. Normal range of Beta hCG <3,5 IE/L. The treatment with arsenic trioxide is marked in grey. The cross represents time of death.

tomography disclosed progression. Addition of oral cyclophosphamide parallel with ATO did not alter the progression and in December 2002 all anti tumoral treatment was stopped. No side effects caused by ATO treatment were observed. The patient was referred to a hospice and died in March 2003.

This case is unusual in several aspects. Firstly, the onset with metastasized extragonadal non-seminomatous cancer is rare. Secondly, the very late relapse, after 13 years, is uncommon and in patients with testicular cancer it comprise less than 5% of the late relapses, as reported by Dieckman et al. [6]. Finally and most importantly, this patient had a therapy resistant disease that despite heavy pretreatment showed a short but obvious response to ATO. This response was manifested as a diminished cough and a clear reduction of β-hCG that lasted for more than 2 months. Obviously, one should be cautious from drawing conclusions from a single patient but on the other hand, this is the only report of clinical effects following treatment with ATO in patients with testicular cancer. Hypothetically, if this patient, who was treated meanwhile SWOG-trial was recruiting patients, had been included in that trial, the SWOG trial would have included 40 patients in order to achieve the statistic power of 92% to detect a clinical response rate $\geq$20% [5].

In summary this letter, in contrast to the SWOG S0207 trial, describes a single patient case with limited but still clear positive clinical and biochemical effects following treatment with ATO. The high frequency of fatal adverse events should however be kept in mind when planning clinical trials in the future. The underlying molecular mechanisms of the anti-tumoral effects following ATO treatment in cisplatinum resistant testicular cancer are unclear and require additional pre-clinical studies.

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