Case Report

Alpha-fetoprotein surge following high-dose chemotherapy in germ cell tumours

Salvatore Luca Burgio¹, Cecilia Menna², Giorgio Papiani², Andrea Casadei Gardini¹, Nicoletta De Luigi¹, Andrea Casadei Gardini¹, Nicoletta De Luigi¹, Roberto Corsi³, Giovanni Rosti⁴

¹Department of Medical Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy, ²Department of Oncology and Hematology, Santa Maria delle Croci Hospital, Ravenna, Italy, ³La Sapienza University, Rome, Italy, ⁴Medical Oncology Department, S. Maria di Ca’ Foncello Hospital, Treviso, Italy

In patients with non-seminomatous germ cell tumours (NSGCTs) who receive chemotherapy and have residual disease, a persistently elevated serum marker level after induction chemotherapy indicates active and progressive disease. High-dose chemotherapy (HDCT) is the standard treatment for patients with relapsed NSGCT. We present a case of a patient with residual disease from NSGCT who showed an increase in serum alpha-fetoprotein levels after HDCT, mimicking progression. Resection of the mass did not show viable cells in the tumour specimen, thus suggesting that the elevated level of the marker was expression of hepatic reconstitution after drug-induced liver damage. HDCT is increasingly used in cases of relapsed NSGCT, and the possibility of treatment-induced alpha-fetoprotein elevation must be taken into account in patient management.

Keywords: Germ cell tumour, Residual mass, Progressive disease, High-dose chemotherapy, Alpha-fetoprotein levels

Introduction

Germ cell tumours are rare neoplasms accounting for less than 1% of all malignancies and are most frequently diagnosed in men in the third decade of life.¹ Mortality has declined markedly since cisplatin was introduced as the basis of chemotherapy in the mid-1970s.² In the cisplatin era, the 10-year survival rate of patients with metastatic non-seminomatous germ cell tumours (NSGCTs) treated with this drug increased significantly from 76% during the period 1977–1986 to 88% in the period 1987–1996.² This improvement resulted mainly from an increase in the survival of patients with poor prognosis and indicates more effective management of NSGCT over time. High-dose chemotherapy (HDCT) with haematopoietic progenitor cell support has led to an approximately 15% improvement in survival of these patients compared to historical data.³–⁶ Moreover, in cisplatin-refractory disease, early tandem HDCT represents the recommended option but is potentially curative in only one-third of these patients.⁷ In NSGCT patients with poor prognosis who receive primary or salvage chemotherapy and show residual disease with negative serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG), radical resection of all residual lesions is mandatory.⁸,⁹ Persistent elevation of serum tumour markers, especially if levels begin to rise even further, is usually expression of progressive disease that requires further chemotherapy, thus delaying surgery. We report the case of an NSGCT patient showing liver toxicity and AFP surge after HDCT to outline the possibility of liver damage as the cause of increased AFP levels.

Case Report

A 25-year-old male was admitted to hospital with severe chest pain and persistent cough. A chest-X-ray revealed a large mass in the anterior mediastinum, confirmed by CT scan (Fig. 1A). A biopsy was performed and mediastinal NSGCT was diagnosed. Histology was not further characterized due to the paucity of biopctic material and necrotic areas. No other sites of disease were detected at whole body CT scan. Laboratory tests revealed elevated serum beta-HCG (13 mUI/ml) and carcinoembryonic antigen (15 mg/dl). The patient underwent induction chemotherapy with cisplatin 20 mg/m² and etoposide 100 mg/m² administered on days 1–5, and bleomycin 30 IU on days 2, 9, and 16 (PEB), at 3-week intervals. Marker negativization was observed after the first course of PEB and a CT scan showed a radiological partial remission after the third treatment course (Fig. 1B). Four weeks after the end of PEB, the patient received cisplatin 20 mg/m² and etoposide.
100 mg/m² on days 1–5 followed by granulocyte-macrophage colony-stimulating factor 5 μg/kg/day to mobilize peripheral blood progenitor cells. Fourteen days after mobilization, 2.7 × 10^6 CD34⁺ cells/kg b.w. were collected by a single leukapheresis and 4 weeks later the patient received a single course of HDCT with carboplatin AUC 20, etoposide 1800 mg/m² and cyclophosphamide 6400 mg/m² divided into four doses given on days 1, 2, 3, and 4. Peripheral blood progenitor cells were reinfused on day 7, followed by granulocyte colony-stimulating factor 5 μg/kg/day until haematopoietic reconstitution. Post-transplant neutropenia <500/μl and thrombocytopenia <20 000/μl lasted 9 and 7 days, respectively. Persistent grade-3 neutropenia was observed for the following 6 weeks. Severe stomatitis was reported for 9 days. On the seventh day after the start of HDCT, the patient showed serum aspartate aminotransferase (AST) 923 U/l and alanine aminotransferase (ALT) 909 U/l, progressively reducing until normalization was reached at +20 days. Although no change in tumour dimension was observed in the CT scan performed 3 weeks after HDCT (Fig. 1C), an increase in AFP (101 ng/ml) was seen at +28 days. For these reasons, surgical resection of the residual mass was postponed. AFP levels normalized after +106 days (Fig. 2) and surgical resection was performed shortly afterwards, the resected residua consisting of fibrosis and necrosis. Five years have passed since the induction chemotherapy and the patient is still disease-free.

Discussion
In patients with poor prognosis NSGCT and post-chemotherapy residual masses, surgical resection is indicated only if serum AFP and beta-HCG levels are within the normal range. A persistently elevated serum marker level after induction chemotherapy is suggestive of progressive disease and salvage therapy is thus contraindicated. Conversely, a small number of studies reported that some patients with persistently elevated serum tumour markers after chemotherapy had locoregional disease and were amenable to surgical resection. Vuky and co-workers reported their single-centre experience of post-chemotherapy surgery in patients with mediastinal NSGCT, highlighting the role of surgery in patients with elevated serum tumour markers. Of the 13 patients who had abnormally elevated markers before surgical resection, three with elevated AFP alone showed long-term survival. Resected residual masses consisted of mature teratoma, necrosis or viable malignant cells. Another study retrospectively reviewed 18 patients with mediastinal NSGCT who were selected for surgical resection in spite of elevated tumour markers after chemotherapy. In this series, only eight patients remained disease-free; all had elevated AFP (median 70, range 26.6–830) but normal beta-HCG pre-resection, and all
In conclusion, increased AFP levels in NSGCT patients must be interpreted with caution when post-chemotherapy liver damage is present. HDCT is increasingly used in these patients and the possibility of treatment-induced false-positive serum AFP elevation must be borne in mind. Strict monitoring of AST/ALT and bilirubin levels after HDCT is recommended to better evaluate any increase in AFP values.

In patients with AFP elevation after HDCT but no clinical–radiological evidence of progression, resection of residual masses can be considered.

Acknowledgement
The authors thank Gráinne Tierney for editing the manuscript.

References
1. Gori S, Porrozo S, Roila F, Gatta G, De Giorgi U, Marangolo M. Germ cell tumours of the testis. Crit Rev Oncol Hematol. 2005;53:141–64.
2. Sonneveld DJ, Hoekstra HH, van Der Graaf WTA, Sluiter WJ, Mulder NH, Willemse PH, et al. Improved long term survival of patients with metastatic nonseminomatous testicular germ cell carcinoma in relation to prognostic classification systems during the cisplatin era. Cancer. 2001;91:1304–15.
3. De Giorgi U, Rosti G, Salvioni R, Papiani G, Ballardini M, Pizzocaro G, et al. Long-term outcome of salvage high-dose chemotherapy in patients with germ cell tumor with poor prognostic features. Urol Oncol. 2011;29:284–90.
4. De Giorgi U, Rosti G, Papiani G, Marangolo M. Long-term follow-up of patients with poor prognosis germ cell tumor treated with early high-dose chemotherapy with hematopoietic progenitor cell support: a single-center experience. Bone Marrow Transplant. 2004;336:639–43.
5. Beyer J, Stenning S, Gerl A, Fossa S, Siegert W. High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumors: a matched-pair analysis. Ann Oncol. 2002;13:599–605.
6. Bokemeyer C, Kollmannsberger C, Meisner C, Hartstrick A, Beyer J, Metzner B, et al. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched-pair analysis. J Clin Oncol. 1999;17:5450–6.
7. Vaena DA, Abonour R, Einhorn LH. Long-term survival after high-dose salvage chemotherapy for germ cell malignancies with adverse prognostic variables. J Clin Oncol. 2003;21:4100–4.
8. De Giorgi, Demirer T, Wandt H, Taverna C, Siegert W, Bornhauser M, et al. Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience. Ann Oncol. 2005;16:146–51.
9. Rick O, Bokemeyer C, Weinknecht S, Schirren J, Pottek T, Hartmann JT, et al. Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. J Clin Oncol. 2004;22:3713–9.
10. Habuchi T, Kamoto T, Hara I, Kawai K, Nakao M, Nonomura N, et al. Factors that influence the results of salvage surgery in patients with chemorefractory germ cell carcinomas with elevated tumor markers. Cancer. 2003;98:1635–42.
11. Vuky J, Bains M, Bacin J, Higgins G, Bajorin DF, Mazumdar M, et al. Role of postchemotherapy adjunctive surgery in the management of patients with nonseminoma arising from the mediastinum. J Clin Oncol. 2001;19:682–8.
12. Kesler KA, Rieger KM, Ganjoor KN, Sharma M, Fineberg NS, Einhorn LH, et al. Primary mediastinal nonseminomatous germ cell tumors: the influence of postchemotherapy pathology on long-term survival after surgery. J Thorac Cardiovasc Surg. 1999;118:692–700.
13. Horn KD, Wax P, Schneider SM, Martin TG, Nine JS, Moraca MA, et al. Biomarkers of liver regeneration allow early prediction of hepatic recovery after acute necrosis. Am J Clin Pathol. 1999;112:351–7.
14 Germa JR, Llanos M, Taberner JM, Mora J. False elevation of alpha-fetoprotein associated with liver dysfunction in germ cell tumors. Cancer. 1993;72:2491–4.

15 Mora J, Garrido A, Antonjuan A, Martínez S, González-Sastre F. Applicability of alpha-fetoprotein-concanavalin A (AFP-ConA) binding to discriminate between germinal or hepatic origin of AFP in germ cell tumour patients during chemotherapy or follow-up. Clin Chem Lab Med. 2007;45:932–933.

16 Morris MJ, Bosl GJ. Recognizing abnormal marker results that do not reflect disease in patients with germ cell tumors. J Urol. 2000;163:796–801.