Acute Leukaemia following High-Dose Chemoradiotherapy with Bone Marrow Rescue for Ovarian Teratoma

A case of acute leukaemia following intensive chemo- and radiotherapy for solid tumour is reported. A 15-year-old girl received four courses of chemotherapy with adriamycin, cyclophosphamide and cis-platinum after the surgical diagnosis of ovarian immature teratoma. An intensification treatment was performed with cyclophosphamide and total body irradiation, followed by marrow rescue. The diagnosis of myelomonocytic acute leukaemia was performed 8 months later. The patient died after a transient improvement following a treatment by hydroxyurea. The roles of the primary tumour, of the chemotherapy and of the marrow transplantation in the occurrence of leukaemia are discussed.

Dr. D. Guyotat, Pavilion Ebis, Hôpital Edouard-Herriot, Place d’Arsonval, F-69374 Lyon (France)

Introduction

High-dose chemotherapy with bone marrow rescue has become a promising approach for the treatment of a variety of solid tumours, such as small cell lung carcinoma, neuroblastoma, testicular and ovarian tumours [1]. Although prolonged thrombocytopenias have been reported following this procedure, even when the marrow is not purged or not cryopreserved [2, 3], the haematological reconstitution is usually satisfactory. We report here a case of autologous transplantation for ovarian malignant teratoma, which was followed by acute non-lymphoblastic leukaemia.

Case Report

A 15-year-old girl presented in February 1983 with acute intestinal occlusive syndrome. A left ovarian tumour was removed. The histologic examination revealed a benign mature teratoma. Serum alpha-fetoprotein and beta human chorionic gonadotrophin were normal, and no further treatment was given. Because of a CT scan revealing again a pelvic mass, a second laparotomy was performed in August 1983, showing an unremovable tumour infiltrating the pelvis and the peritoneum. Biopsies yielded the diagnosis of immature teratoma. Serum alpha-fetoprotein and
beta human chorionic gonadotrophin remained normal. The patient received four courses of chemotherapy with adriamycin (70 mg/m² on day 1), cyclophosphamide (1,200 mg/m² on day 1) and cis-platinum (20 mg/m² on days 1–5). A third look in November 1983 showed the disappearance of the pelvic mass, but the persistence of peritoneal nodules (with a histology of mature teratoma). A bone marrow collection was performed at the end of the surgery for cryopreservation (without marrow purging). The marrow was normal on multiple cytology samples (it was not possible later to perform a karyotype on cryopreserved samples because of the lack of mitoses). The patient received an intensification treatment 3 weeks later by cyclophosphamide (120 mg/kg) and total body irradiation (10 Gy), followed by marrow rescue (1 × 10⁸ nucleated cells/kg infused). The post-transplant blood counts reached 0.5 × 10⁹ granulo-cytes/1 on day 24 and 50 × 10⁹ platelets/1 on day 30. The white cell count increased progressively to normal values, with differentials showing a myeloaemia without blast cells, but a non-regenerative anaemia and a thrombocytopenia persisted. Six months post-transplant, the patient presented with a bilateral pulmonary infection, associated with hyperleucocytosis (52 × 10⁹), and severe thrombocytopenia (14 × 10⁹). The marrow was hypercellular, with an increase in the granulocytic lineage and with very rare megakaryo-cytes, but without abnormal haematological or metastatic cells. The pulmonary infection resolved after antibiotic and antifungal treatment, but blood count abnormalities persisted, with 10% immature cells on differentials. Eight months post-transplant, a marrow aspiration disclosed a 40% involvement of blast cells compatible with the diagnosis of myelomonocytic acute leukaemia. The marrow karyotype was 48, XX, + 8, + M in all mitoses. Serum lysozyme level was 56.2 mg/l (normal: 3–9 mg/l). A transient improvement was obtained after a treatment by hydroxyurea, with disappearance of the peripheral and marrow blast cells, but the marrow karyotype abnormalities persisted, and the blast cells reappeared 6 months later. The patient refused intensive chemotherapy and received only symptomatic treatment. She died in March 1986 of cerebral bleeding.

Acute Leukaemia following ABMT

Discussion

Secondary leukaemia is a well-known complication of chemo- and radiotherapy treatments, especially when alkylating agents are used [4]. It occurs generally more than 1 year after the beginning of chemotherapy, and is often preceded by a pre-leukaemic period [4, 5]. It has also been demonstrated in the dog model that a conditioning regimen with cyclophosphamide and total body irradiation increases the risk of malignancy [6], and a few cases of secondary malignancies have been reported after human allogeneic or syngeneic marrow transplant [7]. To our knowledge, this is however the first reported case of leukaemia after autologous bone marrow transplantation. This case is certainly different from those of leukaemic transformation of engrafted allogeneic marrow cells which have been reported in patients transplanted for leukaemia [7]. Although the clinical presentation and the evolution were similar to those of secondary leukaemia, the interval between the beginning of the chemotherapy and the onset of leukaemia was unusually short in this case. Moreover, one of the karyotypic abnormalities observed in our case (trisomy 8) is common in de novo acute myeloid leukaemia or pre-leukaemic syndromes, but unusual in therapy-related leukaemias [8, 9].
Two factors could have influenced the occurrence of the secondary disease: the primary malignancy and the intensification treatment. The association between testicular or mediastinal germ cell tumours and acute lymphoblastic or non-lymphoblastic leukaemia has been described, the interval between the diagnosis of the solid tumour and the onset of leukaemia being usually less than 1 year [10–13]. In 2 cases, both malignant diseases were diagnosed simultaneously, and it is unlikely that this association could be a mere coincidence [12, 13]. The role of the bone marrow rescue is not clear. From our data, it seems that the marrow was normal at the time of cryopreservation. However, we did not observe a normal haematological reconstitution, and the interval between marrow reinfusion and the diagnosis of the leukaemia was very short. The hypothesis that the conditioning was responsible for the occurrence of the secondary leukaemia is therefore unlikely, but the leukaemic clone present in the cryopreserved marrow or resisting the conditioning regimen possibly had a growth advantage over normal cells after the transplantation.


Peters, W.P.; Eder, J.P.; Bast, R.C.; Schnipper, L.; Frei, E., 111: Novel toxicities associated with high-dose combination alkylating agents and autologous bone marrow support; in Dicke, Spitzer, Zander, Gorin, Autologous bone marrow transplantation, pp. 231–236 (University of Texas, Houston 1985).


