

Complete remission of a high risk metastatic rhabdomyosarcoma in an adolescent treated with a liposomal (Myocet®) regimen

Aurélie Phulpin-Weibel¹, Ludovic Mansuy¹, Valérie Bernier-Chastagner², Marie-Agnès Galloy³, Pierre Bordigoni¹, Pascal Chastagner^{*,1}

¹ Department of Pediatric Oncology, Children's University Hospital, Nancy, France, ² Department of Radiation Therapy, Centre Alexis Vautrin, Nancy, France, ³ Department of Radiology, Children's University Hospital, Nancy, France

Abstract

We report the case of a very high risk metastatic rhabdomyosarcoma teenager treated with an induction therapy using only liposomal doxorubicin (Myocet®) because of his extremely bad health condition. A near complete remission was obtained after 2 courses. Then he received conventional chemotherapy according to the EpSSG protocol, radiotherapy and a reduced-intensity conditioning regimen followed by pheno-identical allogeneic stem cell transplantation. He is in continuous complete remission with a follow-up of nine years.

Keywords: *metastatic rhabdomyosarcoma; liposomal anthracycline*

Introduction

The use of intensive chemotherapy is inevitable to have some chance to cure very high risk sarcomas. However, despite the development of more intensive chemotherapy, the prognosis of metastatic rhabdomyosarcomas remains dismal [1, 2]. For patients in very bad health condition at diagnosis due to organ failures and/or severe infection, these treatments are highly life-threatening and could be sometimes questionable to initiate. Thus, for these patients, the need for agents rapidly active with a minimum of toxicity is crucial.

We present the case of an adolescent treated with the non pegylated liposomal form of anthracycline alone (Myocet®) while he was in a so bad health condition that parents were close to refuse any treatments, and who obtained a near complete remission after two courses. This less toxic form of an agent known to be potentially active is encouraging in treating young patients with a rapidly life threatening cancer.

Case history

A 16-year-old male was referred to our center for a persistent lower back pain, asthenia, anorexia and a left testicular swelling. Physical examination revealed a non-tender huge scrotal mass (13 x 7 cm) associated to enlarged regional lymph nodes. There were no other abnormal physical findings except left Virchow's node (3 x 2 cm).

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*Corresponding author: Pascal Chastagner, MD, PhD, Department of Pediatric Oncology, Children's Hospital, 11 Allée du Morvan 54511, Vandoeuvre, France. Phone: +33 3 83 15 46 37; Fax: 03 83 15 45 51. Email: p.chastagner@chu-nancy.fr

The complete blood count and chemistry were normal except for platelets ($82 \times 10^9/L$) and LDH level (2192 IU/L).

Ultrasonography showed a (13 x 8 x 6.2 cm) paratesticular mass. CT scan revealed mediastinal, diaphragmatic, latero-aortic and coelio-mesenteric lymph nodes. Bone scan showed T8, left iliac and right femoral uptakes. (18)F-FDG PET/CT showed FDG uptake in all lymph nodes detected on CT scan and a diffuse osteo-medullary uptake. Bone-marrow was massively involved by neoplastic cells.

The orchidectomy procedure was performed within 5 days. Resection was microscopically complete; pathological analysis concluded to a paratesticular alveolar rhabdomyosarcoma (aRMS). Neither PAX 3, nor PAX 7-FKHR fusion gene was detected by RT-PCR.

Twenty-four hours after orchidectomy, the patient developed fever ($39^\circ C$), ileus, high blood pressure (160/90 mm Hg) due to ureterohydronephrosis secondary to lymph nodes compression and very bad health condition with loss of 6% of body weight. According to the rapid and severe health alteration (ECOG 4) with organ failures, it was decided not to deliver vincristine, actinomycin and ifosfamide, as recommended using the EpSSG rhabdomyosarcoma protocol, and to initiate chemotherapy using only a liposomal doxorubicin (Myocet®) aiming to be less toxic as possible. A dose of 75 mg/m^2 was delivered in one day over 1.5 hours. Two courses were performed with a 26 days interval. Assessments after these courses revealed a complete response for bone marrow, a decrease in lymph node volumes of 100, 77, and 52% respectively for mediastinal, diaphragmatic and latero-aortic/coelio-mesenteric areas. Pain disappeared within 48 hours, leading to stop analgesic treatments; hypertension and renal impairment resolved within one week. Grade IV vomiting and neutropenia, grade I mucocitis but no cardiotoxicity occurred while a great improvement in health condition was rapidly noticed. These very encouraging results prompted us to continue chemotherapy using 2 IVADo courses (ifosfamide, vincristine, actinomycin, and doxorubicin) followed by 6 courses of ifosfamide + vincristine (IV) and radiotherapy on lymph node areas (50 Gy) and scrotum (41 Gy). After these treatments only

coelio-mesenteric lymph nodes were detected by CT scan while no uptake was seen on FDG/CT. The patient was considered in near complete remission; however, because of the dismal prognosis due to diffuse osteo-medullary and lymph nodes alveolar rhabdomyosarcoma, we proposed a pheno-identical allogeneic hematopoietic peripheral-stem-cell transplantation (HSCT). This was accepted by the teenager and his parents after a specific multidisciplinary informed consent. Pre-transplant reduced-intensity conditioning (RIC) regimen consisted of melphalan at a dose of 140 mg/m^2 , fludarabine 30 mg/m^2 (D-7 to D-3). On day 0, the patient received peripheral hematopoietic stem cells containing $1.95 \times 10^6/\text{kg}$ CD34+ and 2.49×10^7 CD3/kg cells. Graft versus host disease prophylaxis consisted of anti-thymocyte globulin, cyclosporin and mycophenolate mofetil. Hematopoietic reconstitution was achieved by day 23. A sustained complete chimerism profile was documented by D 30. The outcome was uneventful except a grade II acute skin GVHD, successfully treated with two courses of prednisolone. A persistent 100% chimerism profile was obtained. Currently, this patient is disease-free for 9.5 years.

Discussion

Rhabdomyosarcoma, the most common soft tissue sarcoma in adolescents, is a metastatic disease in at least 15% of cases. Despite the development of more intensive chemotherapy including escalating dose and combination of drugs, prognosis has not improved over the last 15 years [1, 2]. A pooled analysis from united states and European cooperative groups reported that the 3-year EFS significantly depends on the number of negative prognostic factors identified as age younger than 1 year or older than 10 years, location in unfavourable site, presence of three or more sites of metastatic disease, and the presence of bone or bone marrow involvement [2].

Our patient presented at diagnosis the three adverse prognostic factors and unfavorable histology leading to an expected five-year EFS less than 5%. Due to ileus, uncontrolled fever and impaired renal function, and his global life-

threatening condition, we preferred not to use aggressive chemotherapy. The very good efficacy of doxorubicin has been demonstrated in an up-front window study in newly diagnosed children with very high-risk metastatic RMS with a response rate of 65% [3]. However, the rapid deterioration of health of this patient prompted us to choose a liposomal form which is known to be less cardio and hematotoxic. Only pegylated liposomal doxorubicin has been tested in children, in a phase I study [4]. Myocet®, a non-pegylated liposomal doxorubicin which has demonstrated reduced cardiac toxicity in adults [5] was chosen because of lack of painful desquamating dermatitis of hands and feet described using the pegylated form of doxorubicin. According to the very good response to Myocet® after two courses, we introduced the IVADo regimen which has been reported to have acceptable toxicity profile and an 82% response rate for alveolar RMS [6].

We performed an allogeneic HSCT because of the dismal prognosis and because delayed tumor regression after HSCT has been reported in a subset of adults with metastatic cancers,

confirming the existence of a graft-versus-tumor effect in solid tumors [7]. To our knowledge, only 6 other cases of high-risk metastatic RMS children treated with allogeneic HSCT, with available data, have been published [9-13]. Conversely to ours, in all these cases myeloablative conditionings followed by allogeneic HSCT with an HLA-identical sibling were used. In accordance with our case, the only 2 patients from the literature who seemed to benefit from allogeneic HSCT are the cases treated with a minimal residual disease after a very good response to conventional chemotherapy [11, 13].

This is, to our knowledge, the first case of high risk metastatic RMS who obtained a near complete remission using Myocet® alone while his life-threatening condition precluded to start intensive chemotherapy. This provides an interesting option to test in a prospective trial for patients who could not receive intensive induction chemotherapy. A phase I study using this less cardiotoxic and potentially less hematotoxic drug is running in France.

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