Two Cases of Adolescents with Paratesticular Rhabdomyosarcoma Inadequately Treated: The Problem of Referral

Andrea Ferrari, MD,¹ Cristina Meazza, MD,¹ Marco Vajna de Pava, MD,¹
Carlo Alfredo Clerici, MD,^{1,2} and Michela Casanova, MD¹

This paper reports on two cases of adolescents with paratesticular embryonal rhabdomyosarcoma completely resected at diagnosis (a pediatric disease potentially curable in more than 90% of cases) and treated at adult facilities with a strategy used for adult soft tissue sarcomas. The final outcome of the two patients was dismal after they received a treatment inconsistent with pediatric protocols. The cases reported here give us a chance to turn the spotlight on a crucial issue—the referral of adolescents with pediatric-type tumors and their access to experienced centers and clinical trials.

Introduction

RHABDOMYOSARCOMA (RMS) IS A HIGHLY MALIGNANT tumor typical of pediatric age. As a result of the systematic use of multidisciplinary risk-adapted treatment programs developed over the years by cooperative international groups, the prognosis for RMS has dramatically improved in the last three decades; two-thirds to three-quarters of children suffering from RMS can now be cured.^{1–4} The survival probabilities are even better for certain subsets of patients, including cases of paratesticular RMS, for which a 5-year overall survival (OS) of around 95% has been described.⁵ However, patient outcomes are strictly influenced by a number of prognostic variables (i.e., histology, local and distant invasiveness, tumor site, and tumor size);^{1–3,6} among them, patient age has emerged as a significant factor influencing survival.^{7,8} Adolescent patients generally have a worse outcome than younger children—this may be related to the higher prevalence of unfavorable features such as alveolar subtype, extremity site, and nodal or distant metastases—but similar to younger pediatric patients, age *per se* is known as an independent prognostic factor.^{7,8}

Albeit rarely, RMS occurs in adults as well. Reports on adult RMS generally describe a disease with a different clinical behavior from that seen in pediatric patients (with a survival rate of only 20–50%).^{9–11} This may be due to a more aggressive biology of the disease in adulthood, but various findings suggest that the different treatments patients receive could at least partially account for such outcome

differences.¹² For example, a study conducted at the Istituto Nazionale Tumori in Milan stratified 171 adult RMS cases according to the appropriateness of their treatment in light of current treatment guidelines for childhood RMS, and found that only 39% had received treatments totally consistent with those adopted in pediatric protocols; when their treatments were comparable with those adopted in children, however, the adults' outcomes resembled that typically seen in pediatric patients (i.e., a 5-year OS greater than 60%).¹³

The suggestion that adults with RMS may have improved outcomes if treated according to pediatric guidelines holds true even more for adolescent patients. Here we describe two very similar cases recently seen at our Unit involving two adolescents with paratesticular embryonal RMS (a disease potentially curable in more than 90% of cases⁵), whose course was dismal after a treatment far from the current protocol recommendations of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG) adopted by all Italian pediatric oncology centers (nine courses of ifosfamide, vincristine, and actinomycin D [IVA] regimen, plus radiotherapy in high-risk cases).¹⁴

Case 1

A 16-year-old male was admitted to a urology unit at a hospital in southern Italy one month after a scrotal mass had appeared, and underwent radical orchiectomy via inguinal incision, with the resection of a mass 7 cm in size. Histology confirmed an embryonal RMS, resected with free histological

¹Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy.

²Faculty of School of Medicine, Department of Biomolecular Sciences and Biotechnology, Section of Psychology, University of Milan, Milan, Italy.

margins, on the strength of which the urologists referred the patient to the local adult medical oncology unit. Staging procedures identified no radiological signs to suggest tumor dissemination. Three courses of chemotherapy with ifosfamide and doxorubicin were administered according to the protocol for adult soft tissue sarcomas. Nine months after treatment completion, retroperitoneal and pulmonary metastases were detected on the computed tomography (CT) scan. The patient was treated to no avail according to a protocol in use for relapsed adult sarcomas with three courses of gemcitabine/docetaxel chemotherapy, and then with three courses of cisplatin plus etoposide. As the tumor progressed further, the patient's parents turned to the Pediatric Oncology Unit of the Istituto Nazionale Tumori in Milan, where the patient was given salvage therapy according to the EpSSG protocol with topotecan, cyclophosphamide, and carboplatin. After an initial partial remission, the tumor began to progress again and the patient died 24 months after diagnosis.

Case 2

A 16-year-old male in southern Italy underwent surgery at the urology unit of a large local hospital to remove a scrotal mass that the patient reported had developed a couple of months earlier. The tumor was resected via an inguinal incision, obtaining microscopically free margins. The diagnosis was embryonal RMS. No staging investigations were performed, and the local oncologist said no further therapies were necessary because the tumor had been completely resected. Five months later, the patient's mother insisted on a CT scan, which revealed retroperitoneal nodal metastases; the family asked to be referred to our unit, where IVA chemotherapy was started. There was no tumor shrinkage after three cycles, so second-line chemotherapy with topotecan, cyclophosphamide, doxorubicin, and carboplatin was administered. Given the evidence of partial tumor remission, the patient underwent retroperitoneal lymph node dissection, followed by radiotherapy to the retroperitoneal nodes. A total of eight courses of chemotherapy were administered, followed by six-month maintenance therapy with vinorelbine and low-dose oral cyclophosphamide. A few weeks after the discontinuation of maintenance therapy, a pelvic relapse associated with multiple lung metastases occurred. Irinotecan and vincristine chemotherapy was administered, followed by surgery and radiotherapy to the pelvis. At the time of writing this paper, the patient shows evidence of further pulmonary progression and is receiving chemotherapy with temozolomide plus oral etoposide and lung irradiation.

Discussion

This paper describes two cases of adolescent patients who unfortunately received the wrong treatment, and in all probability this error has been or soon will be fatal. We suspect that such cases might not be so unusual, and we believe that reporting on them may help to draw attention to the evidence that adolescents and young adults are less likely to gain access to optimal cancer services and to clinical trials.^{15–20} The two cases reported here were seen at our unit at around the same time and have much in common: both patients should have had an excellent prognosis with standard therapy, but after the diagnosis both were referred to an adult oncology service where their RMS was not recognized as a

typical pediatric disease warranting a multidisciplinary approach based on pediatric guidelines. The two patients were treated as having an adult soft tissue sarcoma, which is a very different matter from RMS and requires a completely different treatment approach (e.g., surgery remains the mainstay of treatment and—after resection—chemotherapy is given only in selected high-risk cases, with a regimen different from those adopted for RMS).

The description of the history of these two 16-year-old patients not referred to pediatric oncology facilities and then treated with a therapeutic approach inconsistent with pediatric protocols bring to mind a recent study of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) that looked at the number of 15–19-year-old cancer patients actually treated at AIEOP-affiliated pediatric oncology centers compared to the number of cases expected to occur in Italy based on epidemiological data. The study identified a ratio of observed to expected adolescent cancer cases of only 0.10, as opposed to the 0.77 seen for children up to 14 years old.²¹ A further analysis focusing on RMS showed that fewer than one in three adolescents with RMS were enrolled in AIEOP protocols.²² No data were available on where and how adolescents not seen at AIEOP centers were treated, despite the fact that the AIEOP network involves virtually all pediatric oncology centers in Italy. Though some of these patients may have been treated with pediatric-type strategies, the two cases we describe give us reason to worry about the appropriateness of therapy selected for adolescents with RMS not treated at pediatric oncology centers.

Evidence of AIEOP's failure to enroll adolescents in its trials prompted the creation of an AIEOP Committee on Adolescents. In order to increase the number of adolescents with pediatric tumors referred to AIEOP centers, a major objective of the Committee was to improve awareness at various levels (patient, community, and healthcare system). However, referral to pediatric oncology facilities may be limited in many cases by inflexible upper age limits for admitting patients to pediatric units or enrolling them in clinical trials. A recently launched survey revealed that many Italian children's centers set upper age limits at 16, 15, or even 14 years old²³ (and such centers may have difficulty coping with the two above-described paratesticular RMS patients). The results of this survey would suggest that raising these upper age limits may make pediatric oncology centers more readily accessible to adolescents.²³ As for the age limits for entering clinical trials, all AIEOP protocols are currently open up to 18 or 21 years of age, and the EpSSG protocol for RMS is open up to 25 years of age. But raising the upper age limits for pediatric protocols can only truly help if adult patient groups are included in the project (as, for example, adult physicians may not otherwise hear about the trial). Therefore, there is a strong need to improve cooperation between pediatric oncologists and adult medical oncologists.²⁴ The goal of developing a protocol for adult RMS based on a pediatric-like strategy has recently been achieved by the Italian Sarcoma Group (ISG) and the Rare Tumor Network (mainly concerned with adult oncology) in cooperation with AIEOP.

Acknowledgements

The authors would like to thank the Associazione Italiana per la Ricerca sul Cancro, grant IG 10445, for supporting their

research on rhabdomyosarcoma. The authors would also like to thank the Associazione Bianca Garavaglia for supporting the Youth Project of the Pediatric Oncology Unit of the Istituto Nazionale Tumori of Milan.

Author Disclosure Statement

No competing financial interests exist.

References

1. Raney RB, Anderson JR, Barr FG, *et al.* Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of intergroup rhabdomyosarcoma study group experience and rationale for Intergroup Rhabdomyosarcoma Study V. *J Pediatr Hematol Oncol.* 2001;23:215–220.
2. Stevens MC, Rey A, Bouvet N, *et al.* Treatment of non-metastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology—SIOP Malignant Mesenchymal Tumor 89. *J Clin Oncol.* 2005;23:2618–2628.
3. Arndt CA, Stoner JA, Hawkins DS, *et al.* Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study D9803. *J Clin Oncol.* 2009;27:5182–5188.
4. Sultan I, Ferrari A. Selecting multimodal therapy for rhabdomyosarcoma. *Expert Rev Anticancer Ther.* 2010;10:1285–1301.
5. Ferrari A, Bisogno G, Casanova C, *et al.* Paratesticular rhabdomyosarcoma: report from the Italian and German Cooperative Group. *J Clin Oncol.* 2002;20:449–455.
6. Ferrari A, Miceli R, Meazza C, *et al.* Soft tissue sarcomas of childhood and adolescence: the prognostic role of tumor size in relation to patient body size. *J Clin Oncol.* 2009;27:371–376.
7. La Quaglia MP, Heller G, Ghavimi F, *et al.* The effect of age at diagnosis on outcome in rhabdomyosarcoma. *Cancer.* 1994;73:109–117.
8. Joshi D, Anderson JR, Paidas C, *et al.* Age is an independent prognostic factor in rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Pediatr Blood Cancer.* 2004;42:64–73.
9. Hawkins WG, Hoos A, Antonescu CR, *et al.* Clinicopathologic analysis of patients with adult rhabdomyosarcoma. *Cancer.* 2001;91:794–803.
10. Esnaola NF, Rubin BP, Baldini EH, *et al.* Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. *Cancer.* 2001;91:794–803.
11. Little DJ, Ballo MT, Zagars GK, *et al.* Adult rhabdomyosarcoma: outcome following multimodality treatment. *Cancer.* 2002;95:377–388.
12. Sultan I, Qaddoumi I, Yaser S, *et al.* Comparing adult and pediatric rhabdomyosarcoma in the Surveillance, Epidemiology and End Results Program, 1973 to 2005: an analysis of 2,600 patients. *J Clin Oncol.* 2009;27:3391–3397.
13. Ferrari A, Dileo P, Casanova M, *et al.* Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. *Cancer.* 2003;98:571–580.
14. Ferrari A, Casanova M. Current chemotherapeutic strategies for rhabdomyosarcoma. *Expert Rev Anticancer Ther.* 2005;5:283–294.
15. Bleyer A, Tejada H, Murphy SB, *et al.* National cancer clinical trials: children have equal access; adolescents do not. *J Adolesc Health.* 1997;21:366–373.
16. Bleyer A, Montello M, Budd T, *et al.* National survival trends of young adults with sarcoma: lack of progress is associated with lack of clinical trial participation. *Cancer.* 2005;103:1891–1897.
17. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. *Cancer.* 2006;107:1645–1655.
18. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. *Cancer Treat Rev.* 2007;33:603–608.
19. Burke ME, Albritton K, Marina N. Challenges in the recruitment of adolescents and young adults to cancer clinical trials. *Cancer.* 2007;110:2385–2393.
20. Ferrari A, Montello M, Budd T, *et al.* The challenges of clinical trials for adolescents and young adults with cancer. *Pediatr Blood Cancer.* 2008;50:1101–1104.
21. Ferrari A, Dama E, Pession A, *et al.* Adolescents with cancer in Italy: entry into the national cooperative paediatric oncology group AIEOP trials. *Eur J Cancer.* 2009;45:328–334.
22. Bisogno G, Compostella A, Ferrari A, *et al.* Rhabdomyosarcoma in adolescents: a report from the AIEOP Soft Tissue Sarcoma Committee. *Cancer.* 2011;in press.
23. Ferrari A, Aricò M, Dini G, *et al.* Upper age limits for accessing pediatric oncology centers in Italy: a barrier preventing adolescents with cancer from entering national cooperative AIEOP trials. *Pediatr Hematol Oncol.* 2011;in press.
24. Ferrari A. Harmonizing adult and pediatric approaches to the treatment of soft tissue sarcoma. *Expert Rev Anticancer Ther.* 2009;9:1541–1543.

Address correspondence to:

Andrea Ferrari, MD

Pediatric Oncology Unit

Fondazione IRCCS Istituto Nazionale Tumori

Via G. Venezian, 1

20133 Milan

Italy

E-mail: andrea.ferrari@istitutotumori.mi.it