Rhabdomyosarcoma with unknown primary tumor site. A report from European Pediatric Soft Tissue Sarcoma Study Group (EpSSG)

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Abstract

BACKGROUND: Rhabdomyosarcoma (RMS) is an aggressive malignancy, and 20% of children present with metastases at diagnosis. Patients presenting with disseminated disease very occasionally have no clear evidence of a primary tumor mass. Since these patients have rarely been investigated, we report on a series of patients with RMS and unknown primary tumor site registered in the MTS 2008 protocol (October 2008 - December 2016) coordinated by the European pediatric Soft tissue sarcoma Study Group. METHODS: Patients were administered 9 cycles of induction chemotherapy, and 48 weeks of maintenance chemotherapy. Surgery and/or radiotherapy was planned after the first assessment of tumor response, and implemented after six cycles of chemotherapy. If feasible, radiotherapy to all sites of metastasis was recommended. RESULTS: We identified 10 patients with RMS and unknown primary site, most of them adolescents (median age 15.8 years, range 4.6-20.4). Nine had fusion-positive alveolar RMS. Multiple organ involvement was identified in 7 patients, 2 only had bone marrow disease, and 1 only had leptomeningeal dissemination. All patients were given chemotherapy, 4 were irradiated, and none had surgery. Three patients underwent allogeneic bone marrow transplantation. At the time of this analysis, only 2 patients are alive in complete remission: 1 had received radiotherapy; and 1 had a bone marrow transplant. CONCLUSIONS: RMS with unknown primary tumor occurs mainly in adolescents and is typically fusion-positive alveolar. Radiotherapy may be important, but survival is poor and patients should be offered enrollment in investigational trials.

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Table 1. Patients' characteristics

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Brief running title : rhabdomyosarcoma and unknown origin

Key words: rhabdomyosarcoma, unknown origin, bone marrow

Abbreviations:

RMS	Rhabdomyosarcoma
MTS	Metastatic
EpSSG	European Pediatric Soft Tissue Sarcoma Study Group
CT	Computed tomography
MRI	Magnetic resonance imaging
PET	Positron emission tomography
IVA	Ifosfamide – vincristine - actinomycin D
IVADo	Ifosfamide - vincristine - actinomycin D - doxorubicin
CR	Complete response
PR	Partial response
MR	Minor response
SD	Stable disease
PD	Progression of disease
EFS	Event-free survival

OS Overall survival

ABSTRACT

BACKGROUND: Rhabdomyosarcoma (RMS) is an aggressive malignancy, and 20% of children present with metastases at diagnosis. Patients presenting with disseminated disease very occasionally have no clear evidence of a primary tumor mass. Since these patients have rarely been investigated, we report on a series of patients with RMS and unknown primary tumor site registered in the MTS 2008 protocol (October 2008 - December 2016) coordinated by the European pediatric Soft tissue sarcoma Study Group.

METHODS: Patients were administered 9 cycles of induction chemotherapy, and 48 weeks of maintenance chemotherapy. Surgery and/or radiotherapy was planned after the first assessment of tumor response, and implemented after six cycles of chemotherapy. If feasible, radiotherapy to all sites of metastasis was recommended.

RESULTS: We identified 10 patients with RMS and unknown primary site, most of them adolescents (median age 15.8 years, range 4.6-20.4). Nine had fusion-positive alveolar RMS. Multiple organ involvement was identified in 7 patients, 2 only had bone marrow disease, and 1 only had leptomeningeal dissemination. All patients were given chemotherapy, 4 were irradiated, and none had surgery. Three patients underwent allogeneic bone marrow transplantation. At the time of this analysis, only 2 patients are alive in complete remission: 1 had received radiotherapy; and 1 had a bone marrow transplant.

CONCLUSIONS: RMS with unknown primary tumor occurs mainly in adolescents and is typically fusion-positive alveolar. Radiotherapy may be important, but survival is poor and patients should be offered enrollment in investigational trials.

FULL TEXT

Rhabdomyosarcoma (RMS) is an aggressive malignancy and the most common soft tissue sarcoma in childhood. It can arise from any part of the body, but the commonest sites are the head-neck region (35-40%), genito-urinary tract (20%), and limbs and trunk (20%). Two main histological subtypes are recognized: embryonal RMS (75-80% of cases), and the more aggressive alveolar RMS (20-30%), characterized by the PAX3/7-FOXO1 translocation, which often presents as metastatic at onset. At diagnosis, approximately 20% of children have distant metastases, the most frequent sites being the lungs, bone marrow, bones, and distant lymph nodes. The survival rate for these patients remains unsatisfactory, and less than 30% of patients are cured (1,2).

In a few cases, patients present with disseminated disease, but no evidence of a primary tumor mass, sometimes mimicking other cancers such as acute lymphoblastic leukemia. These cases of RMS with unknown primary tumor site have rarely been investigated, and only a few series and case reports are available in the literature (9-24). A common North American-European analysis on metastatic RMS patients included 12 patients with no evident primary tumor site, whose 3-year event-free survival (EFS) was reportedly 8% (2).

To contribute further information on this rare condition, we report a series of patients with metastatic RMS with unknown primary tumor site registered in the MTS 2008 protocol coordinated by the European pediatric Soft tissue sarcoma Study Group (EpSSG).

PATIENTS AND METHODS

In accordance with EpSSG recommendations, patients with disseminated disease but no evidence of a primary tumor were classified as metastatic and included in the MTS 2008 study. This prospective international trial was conducted from October 2008 to December 2016 (EudraCT, number 2005-000217-35), and enrolled a total of 270 patients from 74 centers in 11 countries. Inclusion criteria were patients under 21 years old with histologically-proven metastatic RMS and no previous treatment. The standard workup included MRI and/or CT of the primary tumor, chest CT scan, and radionuclide bone scan. 18F-FDG-PET/CT was

optional; if performed, the results were used to ascertain tumor extent and establish tumor stage. Staging investigations also included bone marrow aspirates and biopsy. Treatment included 9 cycles of induction chemotherapy: 4 cycles of IVADo (ifosfamide 3 g/m2 on days 1 and 2, vincristine 1.5 mg/m2 weekly during the first 7 weeks, then only on day 1 of each cycle, actinomycin-D 1.5 mg/m2 on day 1, given as a single intravenous injection, and doxorubicin 30 mg/m2 iv. on days 1 and 2) followed by 5 cycles of IVA (same as IVADo, but without any doxorubicin). This was followed by 48 weeks of maintenance chemotherapy with iv. vinorelbine 25 mg/m^{2}on days 1, 8 and 15, and daily oral cyclophosphamide 25 mg/m^2. Tumor response and all sites of metastases was assessed after the 3rd, 6th, and 9th cycles of chemotherapy, and every 3 months afterwards, focused on primary tumor and involved sites.

The response, evaluated after 3 cycles of IVADo chemotherapy, was classified as complete response (CR) = complete disappearance of all visible disease; partial response (PR) = a tumor volume reduction of more than two-thirds; minor response (MR) = a tumor volume reduction of more than one-third but less than two-thirds. A reduction in volume of less than one-third was recorded as stable disease (SD), while an increase in tumor size or the detection of new lesions was classified as progression of disease (PD) (3). Patients with SD were eligible to switch to 2nd line treatment.

Treatment of all sites of metastases (with surgery, radiotherapy or both) was planned after the first tumor response assessment, and implemented after six cycles of chemotherapy (week 19). If feasible, radiotherapy to all sites of metastases was recommended.

All participating centers had to obtain written approval from their local authorities and ethics committees, and written informed consent from patients and/or their parents or legal guardians.

A literature search was also conducted in the PubMed biomedical database. The search was performed as of June 2021 using the keywords “rhabdomyosarcoma” AND “unknown origin”/ “metastatic”/ “leukemia”. Additional papers derived from the references of the articles retrieved were also analyzed. No restrictions were applied regarding date of publication, but only articles written in English were considered. Our inclusion criteria for the review of patients with metastatic rhabdomyosarcoma were: age between 0 and 18 years and a histologically confirmed diagnosis of RMS.

RESULTS

We identified 7 patients with metastatic RMS and no known primary tumor, who accounted for 2.5% of the population enrolled in the MTS 2008 study. We identified 3 more patients whose data were available in the MTS2008 database, but they had been excluded from the analysis conducted for the MTS 2008 study because their diagnosis was established on cytology alone in 1 case, and by center decision in 2. We decided to also include these 3 patients in the present analysis, and the characteristics of all 10 patients are listed in Table 1.

No gender-related difference was noted. Patients were mainly adolescents (median age 15.8 years, range 4.6-20.4). Symptoms were nonspecific and a diagnosis of lymphoma had been suspected in 3 cases (patients 1, 4 and 8) because their symptoms at onset were asthenia, weight loss and lymphadenopathy. One patient presented with disseminated leptomeningeal disease and was diagnosed as RMS NOS based on cell morphology and immunohistochemistry. All other patients had fusion-positive alveolar RMS, positive for PAX3-FOX1 in 8, and for PAX7-FOX1 in 1. Multiple organ involvement was identified in 7 patients, while 2 only had bone marrow disease, and 1 only had leptomeningeal dissemination. The most often involved organs were: bone marrow in 6 cases; and distant nodes in 5. Applying the Oberlin score, which identifies age (<1or>0 years old), unfavorable primary sites (extremity, other site and unknown primary site) bone or bone marrow involvement, and >3 metastatic sites as correlating with a negative prognosis, our series included 1 patient with 1 of these risk factors, 3 patients with 2, 4 patients with 3, and 2 patients with 4 (2). The diagnosis was established from bone marrow aspirates in 4 patients, peritoneal nodules in 2, lymph nodes in 2, a bone biopsy in 1, and cerebrospinal fluid in 1. All patients underwent staging investigations according to the protocol, and 8 were also investigated with FDG-PET/CT (patients x-y and z-a). It emerged that the extremities were not fully investigated with FDG-PET/CT and/or MRI in 3 cases, (patients 3, 4 and 9 in

Table 1).

All patients received chemotherapy according to the protocol. After the first three cycles, 4 patients were in CR, and 3 were in PR, while 1 patient had SD and 1 had PD. One patient with intracardiac tumor died of cardiac arrest before being assessed for tumor response. Radiotherapy was administered to 5 patients (in doses ranging from 41.4 to 50.4 Gy). In particular, the patient with leptomeningeal dissemination received craniospinal irradiation, one patient with peritoneal dissemination received whole abdominal irradiation, two children had radiotherapy to bone lesions and one patient received lymph node irradiation. No patients had surgery. Three patients received an allogeneic bone marrow transplant at the local center's discretion (after bone marrow progression in one case).

At the time of this analysis, 2 patients are alive in CR, 94 and 101 months after their diagnosis. Of the 8 who died, 4 had tumor progression, 2 developed new metastases (1 during treatment), 1 had a cardiac arrest after the first cycle of chemotherapy, and 1 died of transplant-related toxicity (not further specified). One of the two patients still alive received radiotherapy.

DISCUSSION

This report describes a series of patients with no evidence of a primary lesion, and therefore considered as having RMS with unknown primary site. This is a rare condition and represents a diagnostic and therapeutic challenge.

The diagnostic difficulties clearly emerge from our study: despite the usual diagnostic workup (including FDG-PET/CT in 8 cases), clinicians were unable to identify a clear primary lesion in these 10 patients registered in the EpSSG MTS2008 protocol. We know that small tumor lesions localized in the extremities may give widespread dissemination (4), unfortunately 3 patients in our series were not fully investigated in this sense and we cannot exclude they had an unrecognized extremity primary tumor. Careful clinical examination and whole-body MRI or FDG-PET-CT/MRI scanning is suggested for all patients with disseminated RMS if the primary site is not immediately apparent. Another possible limitation of our study concerns the inclusion of a child with disseminated leptomeningeal disease and only a cytological diagnosis: we decided to include this patient in our series because he was considered and treated like a case of metastatic RMS.

The frequent involvement of the bone marrow (it was the only organ involved in 2 cases) may support the hypothesis that it could be the primary tumor site, rather than a site of dissemination. We cannot prove a primary bone or bone marrow origin, but recent studies found that RMS can originate from an aberrant development of non-myogenic cells (5). This would justify the initiation of RMS at sites like the bone marrow and bone.

The treatment of patients with disseminated disease but unknown primary tumor presents a series of obstacles. Local control measures are fundamental in the treatment of RMS, but the absence of a primary lesion often precludes the use of local surgery or radiotherapy, and it is difficult to administer radiotherapy as the disease is frequently widely disseminated and when bone marrow is involved. This is an important aspect as our recent experience suggests that radiation is associated with improved survival in metastatic RMS (6). Chemotherapy was the only treatment modality used in most of our patients, and was unfortunately not enough: only 3 patients in our series are still alive. The predictably poor prognosis may explain why clinicians chose to perform an allogeneic bone marrow transplant in 3 patients, although there is no clear evidence to indicate that it is effective in RMS. Previous trials have shown high dose chemotherapy followed by autologous transplant does not add to survival in metastatic patients (7-8). Since only one of these patients is still alive, we can draw no firm conclusions regarding potential efficacy of this procedure, which carries a small but significant risk of mortality.

The poor prognosis of this group of patients is confirmed by a review of the medical literature. We found 16 publications (from 1976 to the present) describing 22 cases of children with RMS and an unknown primary tumor site (9-24). The characteristics of these patients are summarized in Table 2. As in our series, this condition seemed to be more typical of the fusion-positive alveolar subtype of RMS, and occurred mainly

in adolescents. The most often involved sites were the bone marrow, bone and distant lymph nodes. A lymphoproliferative disease was often suspected, and the diagnosis was made on analyzing the bone marrow. All patients were treated with chemotherapy, while radiotherapy and surgery were performed in a few cases. Only 3 patients out of 17 with outcome data were reportedly alive with no sign of disease, but the follow-up was short.

In conclusion, metastatic RMS with no clear evidence of a primary site is a rare condition, more likely to affect adolescents and to involve the fusion-positive alveolar histotype. Current treatments are rarely able to cure these patients, who should be included in investigational trials along with other very high-risk, metastatic patient groups.

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Conflict of Interest statement

The authors have no conflicts of interest to disclose.

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`Table 1 Patients\selectlanguage{english}' characteristics.docx` available at https://authorea.com/users/368530/articles/567843-rhabdomyosarcoma-with-unknown-primary-tumor-site-a-report-from-european-pediatric-soft-tissue-sarcoma-study-group-epssg

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`Table 2 Reported cases of rhabdomyosarcoma with no identifiable primary soft tissue mass in pediatric a` available at https://authorea.com/users/368530/articles/567843-rhabdomyosarcoma-with-unknown-primary-tumor-site-a-report-from-european-pediatric-soft-tissue-sarcoma-study-group-epssg