HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Pediatr Blood Cancer. 2016 December ; 63(12): 2246–2248. doi:10.1002/pbc.26154.

A Single Center Experience with Undifferentiated Embryonal Sarcoma of the Liver

Melissa D. Mathias, MD[1,*], **Srikanth R. Ambati, MD**[1], **Alexander J. Chou, MD**[1], **Emily K. Slotkin, MD**[1], **Leonard H. Wexler, MD**[1], **Paul A. Meyers, MD**[1], and **Heather Magnan, MD**[1]

[1]Department of Pediatrics, Memorial Sloan Kettering Cancer Center. New York City, New York

Abstract

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare aggressive mesenchymal pediatric tumor. Previously, reported outcomes have been very poor. Here we report a single center experience of 5 patients with UESL treated with upfront gross total resection and adjuvant chemotherapy. We have a median follow up of 8 years with a range from 5 to 19 years with 100% EFS.

Keywords

sarcoma; undifferentiated embryonal sarcoma of the liver; case series

INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is a mesenchymal tumor first described in 1978 by Stocker and Ishak.[1] UESL is an aggressive pediatric tumor classically diagnosed between the ages of 6–10 without gender predominance.[2] It accounts for between 5–15% of pediatric liver tumors.[3–7] Patients commonly present with abdominal mass, pain, and systemic symptoms such as nausea, anorexia and weight loss. Diagnosis is made by a constellation of signs including age, location (primary liver lesion), a panel of undifferentiated pathologic markers including vimentin, desmin, CD10, CD68, α1 anti trypsin, and ruling out of other pathologies.[8–10] Cytogenetic studies have shown a variety of perturbations including gain of chromosome 1q, 5p, 6q, 8p, 12q, and losses of chromosomes 9p, 11p, and 14.[9] Previously, outcomes were very poor. Initial reports described mortality within 12 months of diagnosis and overall survival of <37.5%.[1] However, quicker diagnosis, upfront gross total surgical resection, and adjuvant multiagent chemotherapy has led to improved long-term survival.[3,11–13] Here we report a single institution experience with a

[*]Correspondence to: Melissa Mathias, MD, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. mathiasm@mskcc.org.

CONFLICT OF INTEREST: None

AUTHOR CONTRIBUTIONS: Melissa Mathias had full access to all of the data in this study and takes responsibility for the integrity and accuracy of the data and data analysis. Study Concept and Design: Mathias and Magnan. Acquisition, Analysis, and Interpretation of the Data: All authors. Drafting of the manuscript: Mathias and Magnan. Critical revision of the manuscript for important intellectual content: All authors.

median of 8 years of follow up with a range from 5 to 19 years of follow up with no recurrences or fatalities.

RESULTS

Methods

A retrospective chart review was conducted to identify patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) with the diagnosis of UESL. The data collected included the site and extent of primary disease, metastatic disease evaluation, treatment modalities employed, treatment associated toxicities, and response to treatment. The institutional review board at MSKCC approved the review of medical records for this analysis.

Therapy

All patients were treated with upfront resection followed by multiagent, adjuvant chemotherapy as per previously described institutional “P6” or “EFT” regimens.[14,15] The EFT regimen includes seven cycles of chemotherapy in 21 day cycles. Cycles 1, 2, 3, and 7 are comprised of cyclophosphamide 2100mg/m2/day x 2 days, doxorubicin 37.5mg/m2/day x 2 days and vincristine 2mg/m2/dose x 1 day (capped at 2 mg). Cycles 4, 5, and 6 are comprised of ifosfamide 2800mg/m2/day x 5 days, etoposide 100mg/m2/day x 5 days.[14] The P6 regimen is an older regimen which differs from the EFT regimen in that ifosfamide dosages are 1800mg/m2/day.[15] All cases were reviewed by the treating team to determine whether radiation therapy should be added to the individual treatment plans.

Toxicity

We reviewed electronic medical records including notes and laboratory assessments for all clinic visits and inpatient admissions from diagnosis through last follow up. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Patient Characteristics

Five patients with newly diagnosed, previously untreated UESL were treated at MSKCC between 1997 and 2010. There were two males and three females with a median age of 12 (range 3–16 years). All tumors were located in the right lobe of the liver. Tumors ranged in longest diameter from 6.2 – 15 cm. MSKCC Pathology reviewed each case and determined each patient to have UESL via morphophogy and immunohistochemistry including aplpa-1-antitrypsin, desmin, vimentin staining. No patients had radiographic evidence of metastatic disease. Using Childrens Oncology Group (COG) surgical staging for primary liver tumors at the time of initial surgery, 4 of our patients are classified as having Stage I tumors and 1 patient is classified as having a Stage II tumor.[12]

Treatment

All patients were treated with upfront gross total resection with pathologically confirmed clear margins. All patients received multiagent adjuvant chemotherapy as per the P6 (N=1) or EFT (N=4) regimen. The one patient who received chemotherapy as per P6 was treated

prior to the advent of the EFT regimen at our institution. 1 out of 5 patients did not complete the 7 planned cycles of chemotherapy due to hematologic toxicity. This patient, who has been previously reported, received whole abdominal radiation (2400 cGy) with a boost to the liver (to 3600 cGy) secondary to initial rupture of tumor.[16] Radiation therapy began following cycle 4 and was planned to be given concurrent with cycles 5 and 6 of chemotherapy. This patient never received chemotherapy beyond cycle 4 secondary to a prolonged duration (9 weeks) of grade 3 thrombocytopenia.[16] One patient required a 20% dose reduction of cycle 6 and a 25% dose reduction of cycle 7 due to prolonged grade 3 thrombocytopenia.

Toxicity

Febrile neutropenia was the most common toxicity with 27/32 cycles of chemotherapy (84%) resulting in hospital admission. No patient needed intensive care unit admission or other urgent intervention due to grade 4 febrile neutropenia. While all patients had expected chemotherapy-associated myelosuppression, two patients had prolonged grade 3 thrombocytopenia requiring modifications in treatment plans.

Survival

After a median of 8 years of follow up with a range of 5–19 years, we have a 100 % event-free (EFS) and 100% overall survival (OS) with no recurrences or secondary malignancies.

DISCUSSION

UESL is a rare tumor primarily described in case reports or small case series. Classically a tumor of childhood, there are increasing reports of affected adults.[11,17]

As more institutions share their experiences, it is clear that a radical resection combined with multiagent adjuvant chemotherapy is necessary to improve survival. Reported regimens favor anthracycline and alkylator backbones.[3,13,18] There have also been reports of success with a vincristine, actinomycin-D, and cyclophosphamide regimen.[19] In an older patient, stable disease of metastatic lesions was achieved using a gemcitabine and docetaxel regimen.[17] There exists one case report describing metastatic disease responding to patient derived effector cell infusion.[20] Here we report a single institution experience with encouraging results with extended follow up. Our cohort of patients was treated by primary complete resection followed by treatment with our P6 or EFT regimen. With a median follow up of 8 years , we report 100% OS and EFS, a remarkable outcome for a tumor once uniformly lethal.[1] Our successful upfront resection in the face of localized disease likely contributed to these outcomes. Other single institutions with upfront resections have reported similarly excellent outcomes.[2,12]. The EFT and P6 chemotherapy regimens are more dose intense than other reported regimens. However, the toxicities seen in this series were not outside the range of other combination therapies: myelosuppression and associated febrile neutropenia. It is interesting that patients requiring dose reduction or truncation of cycles did not experience worse outcomes. This could suggest that with adequate primary local control, it may be possible to decrease overall chemotherapy. We need to continue to collect data regarding this rare entity.

Abbreviations

UESL	Undifferentiated Embryonal Sarcoma of the Liver
MSKCC	Memorial Sloan Kettering Cancer Center
CTCAE	Common Terminology Criteria for Adverse Events
OS	Overall Survival
EFS	Event Free Survival

References

1. Stocker JT, Ishak KG. Undifferentiated (embryonal) sarcoma of the liver: report of 31 cases. Cancer. 1978; 42(1):336–348. [PubMed: 208754]
2. Plant AS, Busuttil RW, Rana A, Nelson SD, Auerbach M, Federman NC. A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. J Pediatr Hematol Oncol. 2013; 35(6): 451–455. [PubMed: 23138115]
3. Ismail H, Dembowska-Baginska B, Broniszczak D, et al. Treatment of undifferentiated embryonal sarcoma of the liver in children--single center experience. J Pediatr Surg. 2013; 48(11):2202–2206. [PubMed: 24210186]
4. Lack EE, Schloo BL, Azumi N, Travis WD, Grier HE, Kozakewich HP. Undifferentiated (embryonal) sarcoma of the liver. Clinical and pathologic study of 16 cases with emphasis on immunohistochemical features. Am J Surg Pathol. 1991; 15(1):1–16. [PubMed: 1702267]
5. Sodhi KS, Bekhitt E, Rickert C. Paradoxical hepatic tumor: Undifferentiated embryonal sarcoma of the liver. Indian J Radiol Imaging. 2010; 20(1):69–71. [PubMed: 20352000]
6. Joshi SW, Merchant NH, Jambhekar NA. Primary multilocular cystic undifferentiated (embryonal) sarcoma of the liver in childhood resembling hydatid cyst of the liver. Br J Radiol. 1997; 70:314–316. [PubMed: 9166061]
7. Wei ZG, Tang LF, Chen ZM, Tang HF, Li MJ. Childhood undifferentiated embryonal liver sarcoma: clinical features and immunohistochemistry analysis. J Pediatr Surg. 2008; 43(10):1912–1919. [PubMed: 18926232]
8. Putra J, Ornvold K. Undifferentiated embryonal sarcoma of the liver: a concise review. Arch Pathol Lab Med. 2015; 139(2):269–273. [PubMed: 25611111]
9. Sowery RD, Jensen C, Morrison KB, Horsman DE, Sorensen PH, Webber EM. Comparative genomic hybridization detects multiple chromosomal amplifications and deletions in undifferentiated embryonal sarcoma of the liver. Cancer Genet Cytogenet. 2001; 126(2):128–133. [PubMed: 11376805]
10. Shehata BM, Gupta NA, Katzenstein HM, et al. Undifferentiated embryonal sarcoma of the liver is associated with mesenchymal hamartoma and multiple chromosomal abnormalities: a review of eleven cases. Pediatr Dev Pathol. 2011; 14(2):111–116. [PubMed: 20925497]
11. Pachera S, Nishio H, Takahashi Y, et al. Undifferentiated embryonal sarcoma of the liver: case report and literature survey. J Hepatobiliary Pancreat Surg. 2008; 15(5):536–544. [PubMed: 18836810]
12. Techavichit P, Masand PM, Himes RW, et al. Undifferentiated Embryonal Sarcoma of the Liver (UESL): A Single-Center Experience and Review of the Literature. J Pediatr Hematol Oncol. 2016; 38(4):261–268. [PubMed: 26925712]
13. Cao Q, Ye Z, Chen S, Liu N, Li S, Liu F. Undifferentiated embryonal sarcoma of liver: a multi-institutional experience with 9 cases. Int J Clin Exp Pathol. 2014; 7(12):8647–8656. [PubMed: 25674229]

14. Magnan H, Goodbody CM, Riedel E, Pratilas CA, Wexler LH, Chou AJ. Ifosfamide dose-intensification for patients with metastatic Ewing sarcoma. Pediatr Blood Cancer. 2015; 62(4): 594–597. [PubMed: 25630954]
15. Kolb EA, Kushner BH, Gorlick R, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol. 2003; 21(18):3423–3430. [PubMed: 12972518]
16. Casey DL, Wexler LH, LaQuaglia MP, Meyers PA, Wolden SL. Favorable outcomes after whole abdominopelvic radiation therapy for pediatric and young adult sarcoma. Pediatr Blood Cancer. 2014; 61(9):1565–1569. [PubMed: 24798662]
17. Kallam A, Krishnamurthy J, Kozel J, Shonka N. Undifferentiated Embryonal Sarcoma of Liver. Rare Tumors. 2015; 7(4):6009. [PubMed: 26788276]
18. Bisogno G, Pilz T, Perilongo G, et al. Undifferentiated sarcoma of the liver in childhood: a curable disease. Cancer. 2002; 94(1):252–257. [PubMed: 11815984]
19. May LT, Wang M, Albano E, Garrington T, Dishop M, Macy ME. Undifferentiated sarcoma of the liver: a single institution experience using a uniform treatment approach. J Pediatr Hematol Oncol. 2012; 34(3):e114–e116. [PubMed: 22217489]
20. Xie S, Wu X, Zhang G, et al. Remarkable regression of a lung recurrence from an undifferentiated embryonal sarcoma of the liver treated with a DC vaccine combined with immune cells: a case report. Cell Immunol. 2014; 290(2):185–189. [PubMed: 25038546]

Table 1

Characteristics of Patients with UESL

Patient No	Age	Gender	Year of Diagnosis	Tumor Location	Tumor Diameter	Gross Total Resection	COG Stage	Adjuvant Radiation	Adjuvant Chemotherapy	Outcome (years from diagnosis)	Short Term Toxicity
1	12	M	2010	Right Lobe	6.4 cm	Y + clear margins + tumor rupture prior to surgery	II	2400cGy Whole Abdomen 3600cGy Liver	cyclophosphamide12.6gm/m2; doxorubicin;225mg/m2; ifosfamide 14gm/m2; etoposide 500mg/m2; vincristine 6mg/m2	CR (5 years)	4 febrile neutropenia admissions 9 weeks grade 3 thrombocytopenia
2	17	M	2005	Right Lobe	16.5 cm	Y + clear margins	I	None	cyclophosphamide 15.75 gm/m2; doxorubicin 281mg/m2; ifosfamide 39.2gm/m2; etoposide 1.4gm/m2; vincristine 8mg/m2	CR (7 years)	1 febrile neutropenia admission 4 weeks grade 3 thrombocytopenia
3	3	F	2004	Right Lobe	6.2cm	Y + clear margins	I	None	cyclophosphamide 560mg/kg; doxorubicin 300mg/m2; ifosfamide 42gm/m2; etoposide 1.5gm/m2; vincristine 0.27mg/kg	CR (10 years)	4 febrile neutropenia admissions
4	9	F	1997	Right Lobe	15.0cm	Y + clear margins	I	None	cyclophosphamide 16.8gm/m2; doxorubicin 300mg/m2; ifosfamide 27gm/m2; etoposide 1.5gm/m2; vincristine 8mg/m2	CR (19 years)	4 febrile neutropenia admissions
5	16	F	2007	Right Lobe	14.1 cm	Y + clear margins	I	None	cyclophosphamide 16.8gm/m2; doxorubicin 300mg/m2; ifosfamide 42gm/m2; etoposide 1.5gm/m2; vincristine 8mg/m2	CR (8 years)	5 febrile neutropenia admissions

Pediatr Blood Cancer. Author manuscript; available in PMC 2017 December 01.