Second malignant neoplasms following treatment for hepatoblastoma: an international report and review of the literature

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Abstract

Background: Treatment intensification has improved survival in patients with hepatoblastoma (HB); however, these treatments are associated with an increased risk of late effects including second malignant neoplasms (SMNs). Data is limited regarding SMNs following HB treatment. Methods: Cases of SMNs following treatment for HB reported in the literature and from personal communication were analyzed to further assess this late effect. Results: Thirty-eight patients were identified. Median age at diagnosis of HB was 16 months (range: 3 to 168 months). All patients had received a platinum agent, and almost all had anthracycline exposure. Of 12 patients with a known history of liver transplantation for primary resection of their HB, the majority had post-transplant lymphoproliferative disorder (PTLD) (n=7). The most common SMNs reported were non-PTLD hematopoietic malignancies (n=19). Solid tumors were seen in 12 patients: peripheral neuroectodermal tumor/Ewing sarcoma (3); and one each for renal cell carcinoma, nephroblastoma, colorectal carcinoma, thyroid carcinoma, medulloblastoma, clear cell sarcoma-like tumor, hepatocellular carcinoma, osteosarcoma, and malignant schwannoma. Of 36 patients with data, nineteen survived. Conclusions: SMNs following HB treatment were seen in patients with anthracycline (and cisplatin) exposure, hereditary tumor predisposition syndromes, and/or history of liver transplantation. Hematopoietic malignancies were the most common SMN reported in this cohort and were diagnosed earlier than other SMNs. Prospective collection of data via a companion late effects study or international registry could be used to further evaluate rates and risks of SMNs as well as tumor predisposition syndromes in patients treated for HB.

Introduction

Hepatoblastoma (HB) is the most common malignant liver tumor in children and infants, typically presenting in patients less than 3 years of age.[1] Three-year event free survival has increased to 80-100% in patients with localized disease and 70-80 % for patients with advanced disease and/or metastatic disease.[2-4]With patients

surviving longer, late effects are being increasingly recognized, but little is known about many of these late effects, particularly second malignant neoplasm (SMNs).

For other pediatric tumors, SMNs have been reported from the North American Childhood Cancer Survivorship Study (CCSS), the British CCSS, a Nordic collaborative study and the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer,[5-8]but patients with HB primaries have not been included in these databases. Armstrong et al reported from the CCSS that the most common cause of death in survivors of childhood cancer, excluding primary disease recurrence, was SMNs. They accounted for 46% of the health-related causes of deaths.[9]

In a report of SMNs in pediatric patients in North America, Zong et al reported 7 SMNs out of 815 patients with HB.[10] In a large study of pediatric patients with HB treated in Japan, Ishida et al reported a cumulative incidence of SMNs at 20 years of 8.4%.[11] Specific details regarding the SMNs were generally not reported. Dembowska-Bagińska et al reported on late effects seen in 45 patients treated with HB at their institution over an 18-year period and found a SMN rate of 6.6%.[12] A recent report by Hiyama et al evaluated late effects in 361 patients with HB treated on Japanese Study Group for Pediatric Liver Tumor 2 protocol and found that the risk for SMNs increased with higher pirarubicin dose and lower age at diagnosis.[13]

Exposure to chemotherapeutic agents used in HB treatment (including anthracyclines and alkylating agents), when used to treat other childhood cancers, are known to be associated with increased risk of development of SMNs including myelodysplastic syndrome/leukemias as well as solid tumors.[14-16] Patient specific factors such as age at diagnosis of HB, inherited tumor predisposition syndromes and genetic polymorphisms of metabolizing enzymes may also affect SMN development. Additional data regarding SMN development after HB treatment may help guide future treatment studies with treatment modification strategies to decrease the risk of SMN development while preserving the recently improved rates of cure and surveillance strategies for early detection of SMNs.

Methods

Personal cases from the authors were identified at the authors' local institutions. Institutional review board approval was obtained as per each institution's policy. In addition, the authors reviewed the literature for reported cases of SMNs following treatment for HB by searching PubMed from 1970 through 2020. Keywords used were hepatoblastoma, carcinoma, neoplasm, tumor, malignancy and leukemia. Secondary search of the bibliographies of identified manuscripts was performed. Clinical details, authors and geographic location were utilized to determine and combine duplicated patient reports. Reported cases with similar data and geographic location to previously reported cases were omitted.

Results

Including the current reports, thirty-eight patients with SMNs following treatment for HB have been reported (Tables 1-4).[12-13, 17-32] This included 24 patients from the authors' experiences: acute myeloblastic leukemia (AML), n=7; acute lymphoblastic leukemia (ALL), n=3; myelodysplastic syndrome (MDS), n=2; post-transplant lymphoproliferative disorder (PTLD), n=3; T-cell lymphoma, n=1; renal cell carcinoma, n=1; medulloblastoma, n=1; colon carcinoma, n=1; nephroblastoma, n=1; thyroid carcinoma, n=1, hepatocellular carcinoma, n=1. Seventeen of these 23 patients (Poland-1 to 3, Japan-1 to 12, Germany-1, USA-4) were previously reported but appear here with additional clinical data.[12-13, 24, 29] Four patients were omitted due to lack of sufficient clinical details available to conclude that they had not been reported previously.[10-11, 20, 33]

Reports varied by geographic area with more reports from Asia (n=15) compared with Europe (n=11), North America (n=10), South America (n=1) and combined (n=1). HB was diagnosed at a median age of 16 months (range: 3 to 168 months). Six patients were known to have metastatic disease at diagnosis of HB while 20 were localized, and 12 had no staging data provided. SMNs were diagnosed more often in males than females (M:F ratio 2.2:1). The median time to diagnosis of SMN was 30 months (range: 4 to 240 months), although this estimate lacks precision as there was considerable variation in the definition of this interval. Some authors defined this as the time from diagnosis of HB to the ascertainment of a SMN, while

others timed it from the end of treatment for HB or were not specific in their definition. SMN development fell into three categories: PTLD, non-PTLD hematopoietic malignancies, or hereditary tumor predisposition syndromes (known, suspected or possible). The median time to diagnosis of the subtype of SMN varied according to the type of SMN: PTLD (16.5 months), non-PTLD hematopoietic malignancies (26 months), or known or possible hereditary tumor predisposition syndrome (76 months).

Exposures

All patients had received a platinum agent, and almost all had anthracycline exposure [pirarubicin, n=14; doxorubicin, n=15; tetrahydropyranyladriamycin, n=1; not reported (NR), n=7; none, n=1]. The one patient without anthracycline exposure had PTLD post liver transplantation following chemotherapy (cisplatin/5-fluorouracil/vincristine). At least 8 patients were known to have had etoposide exposure. From 12 of the 24 personal cases with data available, the median cumulative doses of cisplatin and anthracyclines were 397 mg/m2 (range 220 to 770 mg/m2) and 240 mg/m2 (range 150 to 470 mg/m2; doxorubicin) and 310 mg/m2 (range 80-1380 mg/m2; pirarubicin), respectively. Dexrazoxane was known to be used in 3 patients who subsequently developed a SMN. One patient developed a clear cell sarcoma-like tumor of the gastrointestinal tract following radiation that was given post partial hepatectomy, and one patient had hepatocellular carcinoma related to cirrhosis following radiation exposure (implanted seeds at positive margin).

Twelve patients were known to have had liver transplantation for primary resection of their HB. Of those 12 patients, seven had PTLD, four had non-PTLD hematopoietic malignancies (1 each of MDS with MLL rearrangement, AML with monosomy 7; leukemia not otherwise specified; and T cell ALL), and one had thyroid carcinoma. Data on exposures to specific immunosuppression regimes were not available.

Non-PTLD hematopoietic malignancies

Most patients had non-PTLD hematopoietic malignancies (n=19) (Table 1). In this subset of patients, HB was diagnosed at a median age of 13 months (range: 3 to 36 months). SMNs were diagnosed more often in males than females (M:F ratio 2.4:1). Patients were mostly from Japan (n=13) compared with North America (n=3) and Europe (n=3). The median time to diagnosis of SMN in the 7 patients with data was 26 months (range: 7 to 81 months). Chemotherapy agents received by the patients were cisplatin (n=18), pirarubicin (n=12), carboplatin (n=7), doxorubicin (n=5), etoposide (n=5), ifosfamide (n=4), 5-fluorouracil (n=2), vincristine (n=2), and NR (n=2). It is possible that an additional 2 patients from Japan received carboplatin. All 18 patients with data received multi-agent chemotherapy; no patients were reported to have received single agent chemotherapy. Seventeen patients were known to have received anthracycline chemotherapy. At least 4 patients had MDS/leukemia-associated cytogenetic abnormalities (11q23 translocation, n=3; monosomy 7, n=1). Of 18 patients with data, nine died (toxicity, n=4; disease, n=4; NR, n=1). Nine patients were alive at the time of the reports (including one patient alive with disease).

PTLD

Seven patients had PTLD (Table 2). In this subset of patients, HB was diagnosed at a median age of 25 months (range: 15 to 145 months). SMNs were diagnosed more often in males than females (males, n=5; not reported, n=2). No patients were reported from Japan compared with 3 each from North America and Europe; however, PTLD development was not included in the identification of SMN in the Japanese database. One patient was from a report with a combination of different locations. The median time to diagnosis of SMN was 16.5 months (range 4 to 129 months). Chemotherapeutic agents received by the patients were cisplatin (n=4), doxorubicin (n=2), carboplatin (n=2), vincristine (n=2), cyclophosphamide (n=2), 5-fluorouracil (n=1), ifosfamide (n=1), etoposide (n=1), NR (n=3). Of 7 patients with PTLD, four died (3 from disease; 1 NR), and three patients were alive at last follow-up evaluation.

Solid tumors

Twelve patients had solid tumors. The median age at diagnosis of HB was 22 months (range 5 to 168 months), and SMNs were seen slightly more in males than females (M:F 1.2:1). Patients were mostly from

Europe (n=5) compared with North America (n=4), Japan (n=2) and South America (n=1). The median time to diagnosis of SMN was 76 months (range 25 to 276 months). Chemotherapeutic agents received were cisplatin (n=10), doxorubicin (n=9), ifosfamide (n=4), 5-fluorouracil (n=3), pirarubicin (n=2), etoposide (n=2), cyclophosphamide (n=2), vincristine (n=2), irinotecan (n=1), actinomycin (n=1), topotecan (n=1), and NR (n=1). Three patients had familial adenomatous polyposis (FAP)-associated tumors (1 each with colorectal carcinoma, thyroid carcinoma, and medulloblastoma) and one patient with Beckwith-Wiedemann syndrome (BWS) had a nephroblastoma. Seven patients had other solid tumors [primitive neuroectodermal tumor (PNET)]/Ewing sarcoma, n=3; and 1 each of renal cell carcinoma, clear cell sarcoma-like tumor of the gastrointestinal tract, osteosarcoma, malignant schwannoma and hepatocellular carcinoma. These were all tumors that could be seen in hereditary tumor predisposition syndromes like Li-Fraumeni syndrome, neurofibromatosis 2 or other syndrome with a germline mutation. Of 11 patients with data, four died (all of disease). Seven patients were alive at the time of the reports at 12 to 114 months.

Hereditary tumor predisposition syndromes

Four patients had a known inherited tumor predisposition syndrome (FAP, n=1; BWS, n=3) (Table 3). One patient with FAP had colon carcinoma. Two patients with BWS had leukemia, and one had a nephroblastoma. One patient with AML with monosomy 7 was not known to have a hereditary tumor predisposition syndrome but had an uncle with a history of AML. The patient with clear cell sarcoma of the gastrointestinal tract following radiation had two relatives (father, grandmother) with colon carcinoma. The patient with hepatocellular carcinoma following radiation exposure had a BRCA2 mutation identified in the tumor but did not have germline testing done as per the family's preference.

Outcomes

Outcome data from SMNs is limited. Of 36 patients with data, nineteen (53%) survived (non-PTLD hematopoietic malignancies, n=9; solid tumors, n=7; PTLD, n=3). Of the 17 who died, eleven died of disease including two patients with no malignancy directed therapy), four died of toxicity (all with non-PTLD hematopoietic malignancies), and two died with cause of death not reported. Of 13 patients with AML or MDS, twelve had outcome data reported; four died of disease, two died of toxicity, one died (cause not reported), one patient was alive with disease, and four were alive at the time of the reports.

Toxicity-related deaths followed treatment for ALL (n=2) and AML (n=2). Of the 2 patients with ALL, one died of bronchiolitis obliterans 8 months after stem cell transplant, and one died of sepsis 2 months from diagnosis of ALL. The 2 patients with AML had both been initially treated for metastatic HB with multi-agent chemotherapy regimens in combination with liver transplantation. Stem cell transplant was planned for both patients for treatment of their AML; however, one patient had cardiopulmonary arrest during the conditioning regimen and died later due to multi-organ failure. The other patient with AML had severe chronic graft versus host disease following allogeneic stem cell transplant including possible bronchiolitis obliterans as well as membranoproliferative glomerulonephritis with renal failure and cardiomyopathy. This patient died six years post stem cell transplant due to cardiac arrest from heart failure (and resultant multi-organ failure) related to culture negative sepsis.

Discussion

SMNs following treatment for HB occur at a rate that is undetermined. The lack of a denominator makes calculation of a rate using this series impossible. Rates of SMN development after HB treatment have been reported between 1 and 8.4% of patients.[10-13] SMNs after HB that have been reported to date seem to occur in three distinct patterns: patients with anthracycline (and cisplatin) exposure, BWS or FAP diagnosis (or clinically consistent with possible hereditary syndrome), and/or history of liver transplantation. In addition, two patients had SMNs following radiation exposure.

Hematopoietic malignancies were the most common SMN reported and appeared to be diagnosed earlier than other SMNs in this cohort. Nineteen patients developed non-PTLD hematopoietic malignancies post HB treatment. Twelve had received pirarubicin, and at least four patients had cytogenetic abnormalities

(11q23 translocation, n=3; monosomy 7, n=1). Exposure to cisplatin and anthracyclines is known to increase the risk of SMN.[34-36] In our cohort for patients with hematologic SMNs, cumulative anthracycline dose was 190 mg/m2 doxorubicin (range 150 to 360 mg/m2). A cumulative anthracycline dose more than 170 mg/m2 has been associated with an increased risk of development of therapy related MDS/AML.[20, 37] Hiyama et al reported previously (in their 13 patients included in this study) a significant correlation between cumulative dose of pirarubicin with SMN development following HB treatment.[13] Further analysis could help to determine if pirarubicin is more likely to increase the risk of SMN compared with doxorubicin in patients with HB. Exposure to the leukemogenic agent etoposide was less common in this cohort (n=8) and was associated with development of solid tumors (n=2; thyroid carcinoma, Ewing sarcoma) and non-PTLD hematopoietic malignancies (n=6). Clinical features of AML following chemotherapy varies by initial exposure to alkylating agents (latency 5-8 years, prior MDS, abnormalities of chromosomes 5 and 7) versus topoisomerase inhibitors (less than 3 years, no prior MDS, 11q23 abnormalities).[37-40] As noted above, in our cohort, 6 patients with etoposide exposure developed non-PTLD hematopoietic malignancies.

Chemotherapeutic exposure can also increase the risk of development of secondary solid tumors, but it is usually seen at a longer latency period of over 10 years.[38] Cisplatin has been associated with an increased risk of SMN following treatment for other malignancies.[41-43] No SMNs were reported following cisplatin monotherapy for HB (although longer follow up is needed to confirm this finding). Anthracyclines have also been associated with an increased risk of solid tumor SMNs including breast cancer (though this association is likely related to inherited tumor predisposition with germline TP53 mutation).[36,44] Four patients were known to have tumor predisposition syndromes (FAP, n=1; BWS, n=3). Two SMNs seen in these patients were tumors that were less likely to have been related to prior treatment (thyroid carcinoma, n=1; colon carcinoma, n=1) and more likely related to the underlying tumor predisposition syndrome; conversely, two patients with BWS developed AML.

PTLD following liver transplant is fairly common and is especially problematic in the setting of an Epstein-Barr virus (EBV) naïve patient receiving a liver from an EBV positive donor. It is considered an early malignancy and is associated with T cell depletion and EBV reactivation. Seven patients in our cohort had PTLD at a median of 16.5 months following transplant which is shorter than the timing of PTLD development for all solid tumors (approximately 5 years).[45] Risk for PTLD is multifactorial. Without data on immunosuppression in this cohort, the impact of immunosuppression in combination with post transplantation chemotherapy for patients with HB remains to be determined.[30,46]Modification of chemotherapy and/or immunosuppression post transplantation could potentially decrease the risk for SMNs for this cohort. It is possible that patients receiving HB chemotherapy prior to liver transplant are more susceptible to PTLD development compared with liver transplant recipients who have not received prior chemotherapy. This could be assessed in a future study with a control group of pediatric liver transplant recipients without previous chemotherapy exposure.

Risk factors in SMNs following treatment of other pediatric tumors include gender and age at time of treatment exposure.[47] Lower age at the time of diagnosis of HB was seen in the 13 patients from Japan when compared to patients who did not have a SMN.[13] In addition, they reported an increased risk of SMN development in patients who received higher doses of pirarubicin.

In this cohort, all four of the toxicity-related deaths occurred in patients with hematopoietic malignancies. Treatment of SMNs can be complicated by previous cytotoxic chemotherapy (including high cumulative anthracycline dose). This can be particularly difficult with a cumulative doxorubicin dose of 360 mg/m2 or higher following HB treatment and then having a subsequent need for anthracyclines in treatment of many of the noted SMNs (Ewing sarcoma, AML, ALL). Increased risk of nephrotoxicity due to prior cisplatin exposures and potentially unrecognized cumulative toxicity may also contribute to excess mortality during treatment for SMN.

Geographic influence on the risk of SMN development is difficult to determine because of mostly anecdotal data, but two population studies out of Japan reported 3.9% and 8.4% SMNs of survivors of HB, and one population study out of Poland reported a rate of 6.6% compared with 1% on a study out of North

America.[10-13] Geographic differences in development of SMNs in patients with HB could be related to specific chemotherapy agents, cumulative doses, geography influenced exposures, genetic polymorphisms of metabolizing enzymes and/or other factors.[48-49]

Treatment era may also have an effect with an initial increase in SMNs after the improved rate of cure with multiagent chemotherapy followed by a subsequent decrease in SMNs with further advances in risk stratification and treatment reduction. Given that this population is still quite young, it will take time to determine if these subsequent changes in HB treatment will decrease the SMN incidence.[7,13]

Weaknesses of this report include the retrospective nature of the study, the lack of complete data for all patients and the lack of central pathology review. Central pathology review in current studies has demonstrated biologic heterogeneity in liver tumors thought to be standard HB. It is not possible to know if some of the SMNs in our review developed in patients who would currently not be classified as standard HB (for example, hepatocellular neoplasm not otherwise specified or malignant rhabdoid tumor of the liver). Supportive care and tumor directed therapies have improved considerably from the treatment era of many of these patients; thus, the current risk and rate of development of SMN are unable to be predicted. Nonetheless, patients received the conventional agents used in HB treatment: cisplatin (all patients) and an anthracycline (all but 1 patient). Another potential, but unavoidable, weakness of the report is the lack of sufficient numbers of patients receiving either doxorubicin or pirarubicin to permit a statistically valid evaluation of any difference in risk of SMN development comparing one anthracycline to the other.

This study has significant limitations. Without a control group, certain analyses are impossible. The incidence, timing and causative associations of SMNs after treatment for HB remain to be determined. Nonetheless, certain observations can be made. SMNs were seen in three different groups of patients: patients exposed to anthracycline (and cisplatin) exposure, patients with BWS or FAP diagnosis, and/or history of liver transplantation. In addition, two patients developed SMNs following radiation exposure. Hematopoietic malignancies were the most common SMN reported (with most AML or MDS), and a longer latency was seen for development of solid tumor SMNs (median time of 76 months versus 26 months for hematologic SMNs). Observed survival for SMNs was slightly greater than 50%.

Given improved survival rates after HB treatment and longer follow up time, SMN development becomes an increasingly significant concern. Current incidence estimates are almost certainly too low. Further assessment of specific risk factors for SMN post HB treatment warrant evaluation with larger numbers of patients and longer time of follow up to allow for evaluation of patients at older ages. Future evaluation of potential ethnic and/or geographic differences in types and numbers of SMNs could be evaluated following treatment on the current open international hepatoblastoma trial (PHITT/AHEP1531). In addition, development of SMN following multi-agent chemotherapy versus cisplatin monotherapy could be assessed. Prospective collection of data and tissue for molecular sequencing via a companion late effects study or international registry could be used to more accurately evaluate rates and risks of SMNs. Quality-adjusted life years in survivors and correlation with tumor predisposition syndromes in patients treated for HB could also be examined. Additional surveillance time and SMN data as survivors reach older ages can help guide future trials in terms of upfront treatment reductions and surveillance approaches for survivors with the aim of a resultant decreased risk of late mortality.

Conflicts of interest: We declare no conflicts of interest.

Data availability statement: Data available on request from the authors.

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Legends

TABLE 1 Clinical characteristics of patients with (non-PTLD) hematologic malignancies following treatment for hepatoblastoma

TABLE 2 Clinical characteristics of patients with solid tumors with known or possible tumor predisposition syndrome following treatment for hepatoblastoma

TABLE 3. Clinical characteristics of patients with post-transplant lymphoproliferative disorder following treatment for hepatoblastoma

TABLE 4 Clinical characteristics subgroups of patients with second malignant neoplasms following hepatoblastoma treatment

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