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Minimal adjuvant chemotherapy for children with hepatoblastoma resected at diagnosis (AHEP0731): a Children's Oncology Group, multicentre, phase 3 trial

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Data sharing

The Children's Oncology Group Data Sharing policy describes the release and use of Children's Oncology Group individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) guidelines. Only data expressly released from the oversight of the relevant Children's Oncology Group Data and Safety Monitoring Committee are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP data archive. Data are available to researchers who wish to analyse the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analysed in the primary results paper can be expected to be available upon request. Requests for access to Children's Oncology Group protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by Children's Oncology Group to be feasible and of scientific merit, and who agree to the terms and conditions of use. For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial done under a binding collaborative agreement between the Children's Oncology Group or the NCI Cancer Therapy Evaluation Program and a pharmaceutical or biotechnology company must comply with the data sharing terms of the binding collaborative or contractual agreement and must receive the proper approvals.

Declaration of interests

The other authors declare no competing interests.

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Summary

Background—Hepatoblastoma treatment with curative intent requires surgical resection, but only about a third of newly diagnosed patients with hepatoblastoma have resectable disease at diagnosis. Patients who have upfront resection typically receive a total of 4–6 cycles of adjuvant chemotherapy post-surgery, with the combination of cisplatin, fluorouracil, and vincristine. We aimed to investigate whether event-free survival in children with hepatoblastoma who had complete resection at diagnosis could be maintained with two cycles of adjuvant chemotherapy.

Methods—In this Children's Oncology Group, multicentre, phase 3 trial, patients were enrolled in four risk groups on the basis of Evans surgical stage, tumour histology, and levels of α -fetoprotein at diagnosis to receive risk-adapted therapy. Here, we report on the low-risk stratum of the trial. Eligible patients were younger than 21 years and had histologically confirmed, stage I or II hepatoblastoma without 100% pure fetal stage I or small-cell undifferentiated histology; elevated serum α -fetoprotein level (>100 ng/mL); a complete resection at diagnosis; at least 50% Karnofsky (patients >16 years) or Lansky (patients ≤ 16 years) performance status; and had received no previous chemotherapy or other hepatoblastoma-directed therapy. Patients received two 21-day cycles of cisplatin, fluorouracil, and vincristine within 42 days of resection, consisting

of cisplatin (100 mg/m² per dose or 3.3 mg/kg per dose for children <10 kg) intravenously over 6 h on day 1; fluorouracil (600 mg/m² per dose or 20 mg/kg per dose for children <10 kg) intravenous push on day 2; and vincristine (1.5 mg/m² per day to a maximum dose of 2 mg, or 0.05 mg/kg per day for children <10 kg) intravenous push on days 2, 9, and 16. The primary outcome was investigator-assessed event-free survival. As prespecified by protocol, we analysed the primary endpoint 6 years after enrolment (cutoff date Dec 31, 2017). This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number [ClinicalTrials.gov](https://clinicaltrials.gov) NCT00980460, and is now permanently closed to accrual.

Findings—Between May 18, 2010, and May 28, 2014, 51 patients in 32 centres in two countries were enrolled into the low-risk stratum of this trial, of whom 49 received chemotherapy treatment after surgery and were evaluable for activity and safety. Median follow-up time for all evaluable patients was 42 months (IQR 36–62). 4-year event-free survival was 92% (95% CI 79–97) and 5-year event-free survival was 88% (72–95). Two (4%) of 49 patients had surgical complications (bile leaks). The most common grade 3–4 adverse events were febrile neutropenia in seven (14%) patients, decreased neutrophil count in three (6%) patients, infections in four (8%) patients, and diarrhoea in four (8%) patients. Ototoxicity occurred in one (2%) patient. One (2%) patient of the three who relapsed in this cohort died from disease. Two (4%) patients died in clinical remission after therapy discontinuation. One patient died of pneumonia and bacterial sepsis 1 year after therapy discontinuation and another patient died of unrelated causes 57 months after therapy completion. There were no treatment-related deaths.

Interpretation—Minimal postoperative chemotherapy with two cycles of cisplatin, fluorouracil, and vincristine can ensure disease control in patients with hepatoblastoma resected at diagnosis. Our results show that dose reduction of ototoxic agents is a safe, effective treatment for these children.

Introduction

Hepatoblastoma is the most common liver malignancy in children and approximately 100–125 new cases are diagnosed yearly in North America.¹ Complete resection is done with curative intent; however, most children present with locally advanced tumours and are treated with chemotherapy before surgical resection.² A subset of patients with localised disease can be resected at diagnosis, and Ortega and colleagues³ reported a 5-year event-free survival of 91% with four cycles of moderate intensity postoperative chemotherapy in patients with stage I and II disease. Douglass and colleagues⁴ reported a 5-year event-free survival of 91% in patients with stage I disease and 100% in patients with stage II disease. Patients with localised, initially unresectable tumours who have delayed resection after neoadjuvant therapy have equivalent outcomes to patients treated with upfront resection followed by chemotherapy, but the former receive higher cumulative doses of chemotherapy, and therefore have higher risk for chemotherapy-related complications.³ Postoperative chemotherapy has been a routine component of hepatoblastoma therapy, but the optimal number of cycles and cumulative dose needed after resection at diagnosis has not been determined.

The International Childhood Liver Tumors Strategy Group (SIOPEL) studies of hepatoblastoma have favoured the use of preoperative chemotherapy and delayed resection

for all patients to minimise surgical morbidity, although this approach usually results in higher cumulative doses of administered chemotherapy.⁵⁻⁷ Conversely, the Children's Oncology Group (COG) has advocated for resection at diagnosis, when feasible (patients with stage I and II disease), to allow for detailed pathological assessment of untreated tumours, improved tailoring of therapy, and reduced cumulative doses of chemotherapy.¹ This approach has been associated with a relatively low incidence of surgical morbidity.^{2,8}

The SIOPEL 3 clinical trial (NCT00003912) showed that cisplatin monotherapy was effective for treating standard-risk patients with hepatoblastoma, and included several patients with tumours that would have been amenable to resection at diagnosis according to COG surgical guidelines.⁶ These children received a cumulative dose of cisplatin (480 mg/m²) that was substantial enough to cause long-term hearing complications in a group of patients.^{5,6} The standard of care for patients with completely resected tumors at diagnosis on COG trials has been the use of four cycles of cisplatin (100 mg/m² per dose), fluorouracil, and vincristine.⁴ This cumulative cisplatin dose is slightly lower than administered in the SIOPEL 3 trial. The COG trial, P9645 (NCT00003994), did not show any benefit of administering amifostine before cisplatin in decreasing ototoxicity.³ On the basis of these data, the present COG trial, AHEP0731 (NCT00980460), included a specific subgroup of patients to test if chemotherapy with cisplatin (100 mg/m² per dose), fluorouracil, and vincristine could be safely reduced from four to two cycles while maintaining the event-free survival outcomes for patients who had resection at diagnosis.

Methods

Study design and participants

The AHEP0731 trial was designed to test a risk-based treatment approach for children with hepatoblastoma, to diminish toxicity in low-risk patients, improve survival in intermediate-risk patients, and identify new agents that may be used in high-risk and recurrent patients. Eligible patients were assigned on the basis of Evans surgical stage, tumour histology, and serum α -fetoprotein levels at diagnosis to four risk treatment categories: very low-risk, patients with stage I pure fetal histology hepatoblastoma; low risk, patients with stage I or II, non-small-cell undifferentiated disease; intermediate risk, patients with stage I or II small-cell undifferentiated histology, or any stage III hepatoblastoma; and high risk, patients with stage IV disease hepatoblastoma and those with any stage disease and α -fetoprotein levels less than 100 ng/mL (see protocol in the appendix). Here, we report on the results of patients assigned to the low-risk group of the trial. Other risk groups will be reported elsewhere.

Eligible patients were younger than 21 years and had histologically confirmed, Evans surgical stage I or II hepatoblastoma without 100% pure fetal histology or small-cell undifferentiated histology; elevated serum α -fetoprotein level (>100 ng/mL); a complete resection at diagnosis; at least 50% Karnofsky (patients >16 years) or Lansky (patients 16 years) performance status; and had received no previous chemotherapy or other hepatoblastoma-directed therapy. Patients also had to have adequate liver, bone marrow and renal functions (appendix).

The National Cancer Institute, the Pediatric Central Institutional Review Board, and the institutional review boards of the participating institutions approved the protocol. Written informed consent was obtained for all patients before starting protocol therapy, according to Department of Health and Human Services guidelines.

Procedures

At diagnosis, CT or MRI of the primary tumour, according to institutional preference, and a chest CT to assess for metastatic disease were done. Assignment of the Pretreatment Extent of Disease (PRETEXT) group (I, II, III, or IV) and PRETEXT annotation factors was done on the basis of the imaging results by the treating institution for all patients at diagnosis (appendix). PRETEXT was not to be used for risk classification but was to guide the surgical approach, specifically using PRETEXT group and annotation factors to determine which patients should be considered resectable or unresectable at diagnosis. All treatment decisions were made according to local interpretation of imaging studies. All radiological images were centrally reviewed, retrospectively, by a consensus of the study committee radiologists and surgeons.

The study provided permissive surgical guidelines that recommended upfront resection at diagnosis for PRETEXT I and II lesions if there was a preoperative radiographic margin of more than 1 cm from the middle hepatic vein (ie, at least two of the three major hepatic veins would be preserved), the retrohepatic inferior vena cava (V), and the bifurcation of the portal vein (P). Retrospectively, the proximity of the tumour to the major liver vasculature was centrally reviewed and coded as negative (if the distance from the tumour to these vessels was >1 cm), 0 (if the tumour was within 1 cm), 1 (if the tumour was touching), 2 (if the tumour was distorting, displacing, or encasing the vessels), or 3 (if there was radiographically identifiable tumour thrombus within the lumen of these major vessels). The V and P definitions used in this study were specifically used to centrally review and define surgical resectability. The V and P definitions in this study were not the same definitions as those used in past SIOPEL studies or the new international liver tumour risk classification scheme. In comparing the terminology used in this study to the definitions used in past SIOPEL studies and the new international liver tumour study, the V2 and V3 categories correspond with V positive, and the P2 and P3 categories correspond with P positive. Surgical decisions were not protocol-mandated, and resection at diagnosis irrespective of PRETEXT assignment was ultimately at the discretion of the treating institution. Information was collected about surgery-associated complications to justify the approach used in this study.

Baseline physical examinations, organ function, α -fetoprotein levels, and imaging studies were done before therapy. Imaging could be done before study enrolment, but if start of therapy was delayed by 28 days or longer then additional imaging was required before therapy. Serial α -fetoprotein levels were to be drawn before each cycle and during each follow-up reporting period. A complete response was considered as the resolution of all lesions and a normal α -fetoprotein level according to institutional standards and normal ranges.

Patients were staged for risk classification with Evans surgical staging guidelines⁴ before the initiation of chemotherapy, as either stage I (complete resection with microscopically negative margins) or stage II (complete resection with microscopic residual disease at the margins of resection or preoperative or intraoperative tumour rupture).

Rapid central pathological review before study enrolment was required for all primarily resected specimens to assess tumour histology and the presence of positive surgical margins. Central review was mandated before enrolment to confirm the diagnosis of very low risk patients with stage I 100% pure fetal histology as a safety measure for patients who were to receive no chemotherapy after surgery, to rule these patients out. If patients had small-cell undifferentiated elements not identified locally and only identified after central pathological review, they were classified as low-risk according to the local assessment and were eligible to receive two cycles of cisplatin, fluorouracil, and vincristine.

After recovery from the hepatic resection and within 42 days, patients received two cycles of cisplatin, fluorouracil, and vincristine chemotherapy, which consisted of cisplatin (100 mg/m² per dose or 3.3 mg/kg per dose for children <10 kg) intravenously over 6 h on day 1; fluorouracil (600 mg/m² per dose or 20 mg/kg per dose for children <10 kg) intravenous push on day 2; and vincristine (1.5 mg/m² per day, maximum dose 2 mg, or 0.05 mg/kg per day for children <10 kg) intravenous push on days 2, 9, and 16. A second cycle of cisplatin, fluorouracil, and vincristine was repeated in 21 days (appendix). Dose reductions and modifications were allowed per protocol (appendix). Repeat imaging and α -fetoprotein measurements were done after two cycles of therapy, when all patients were assessed for end of therapy response.

The maximum grade of each toxicity type observed during protocol therapy was reported, provided the grade was 3, 4, or 5 according to National Cancer Institute Common Toxicity criteria guidelines (versions 3 and 4).

Outcomes

The primary outcome of the stratum reported here (children with low-risk hepatoblastoma) was investigator-assessed event-free survival, defined as the time from enrolment to disease progression, diagnosis of a second malignant neoplasm, death from any cause, or last patient contact without the occurrence of any of these noted analytical events. Primary objectives for other risk strata within the trial are listed in the appendix.

Secondary objectives of the study included to determine if PRETEXT grouping could predict tumour resectability; to monitor the concordance between institutional assessment of PRETEXT grouping and PRETEXT grouping as done by expert panel central review; and to determine the proportion and estimate the event-free survival of patients with potentially poor prognostic factors, including α -fetoprotein levels of less than 100 ng/mL at diagnosis, microscopic positive surgical margins, surgical complications, multifocal tumours, microscopic vascular invasion, macrotrabecular histological subtype, and small-cell undifferentiated histological subtype. These outcomes will be reported elsewhere.

Statistical analysis

The prespecified design objectives were different for the four risk categories. For the low-risk stratum reported here, we expected to accrue 9.2 patients per year for 5 years and follow them for an additional year, by which time we expect most disease-related analytic events will have occurred, recruiting a total of 51 patients. We analysed the primary endpoint after 6 years (5 years after enrolment and 1 year of follow-up; cutoff date Dec 31, 2017). If eight or more events were observed during the first year of follow-up, we considered the strategy of surgery with reduced chemotherapy to show insufficient disease control. The protocol contains a typographical error in the cutoff value as seven events; this error was not corrected (appendix). If protocol therapy was associated with a long-term event-free survival of 78%, it would be identified with insufficient disease control with a probability of 0.90. If protocol therapy was associated with long-term event-free survival of 89%, it would be accepted as having sufficient disease control with a probability of 0.81.

The study data were submitted for interim monitoring to the COG data safety monitoring committee every 6 months. At each instance, the study statistician reported whether a conclusion regarding the feasibility of treatment plan, as described above, could be determined.

Eligible patients who received the first dose of chemotherapy within 42 days of surgical resection were analysed for activity and safety. Overall survival was analysed post hoc and defined as the time from enrolment to death or last confirmed patient contact alive. All other patients were censored at last contact. We estimated event-free survival and overall survival as a function of time since enrolment using the Kaplan-Meier method.⁹ We used complementary log-log transformation to calculate 95% CIs.¹⁰ We estimated follow-up time using the method of Schemper and Smith.¹¹ For each secondary analysis, we excluded any patient whose data were missing for that particular characteristic; we did not impute missing data. We used the rapid central pathology review to determine the presence of pure fetal histology and the central review of PRETEXT staging and PRETEXT annotation factors in describing patient outcome for this report. We did prespecified analyses of patients with stage I and stage II disease who had tumours that were in close proximity to the crucial hepatic vasculature, as well as subgroup analyses of event-free and overall survival according to age, sex, and α -fetoprotein level at diagnosis. We did all analyses using SAS (version 9.4) and STATA (version 15).

This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00980460, and is now permanently closed to accrual.

Results

Between May 18, 2010, and May 28, 2014, 51 patients in 32 centres in two countries were included in the low-risk stratum of the trial, of whom 49 (96%) were evaluable for activity and safety (figure 1).

Baseline characteristics are in table 1. The median age at diagnosis was 16 months (range 0–96). Median α -fetoprotein level at diagnosis was 14 086 ng/mL (range 104–391 410 ng/mL),

excluding one patient who did not have a baseline value. Two (4%) of 48 patients with baseline α -fetoprotein level did not normalise α -fetoprotein: one patient relapsed 89 days after enrolment and before normalisation of α -fetoprotein, whereas another patient was lost to follow-up 446 days after enrolment without normalisation of α -fetoprotein. α -Fetoprotein values normalised in the remaining 46 (96%) patients with baseline values as follows: 25 (54%) of 46 patients by the conclusion of therapy, 16 (35%) patients within 6 months of therapy discontinuation, four (9%) patients between 6 and 12 months of therapy discontinuation, and one (2%) patient beyond 1 year after therapy discontinuation. In a post-hoc analysis, there was no difference in outcome on the basis of the timing of α -fetoprotein normalisation (data not shown). Of three (6%) of 49 patients with recurrent disease, two normalised α -fetoprotein by the end of therapy and the third had an end of therapy level of 15 ng/mL (institutional upper limit of normal 8 ng/mL), and each had a subsequent progressive increase of α -fetoprotein. Minor transient increases in α -fetoprotein levels (<100 ng/mL) that returned to normal were observed both on and after therapy discontinuation in patients who ultimately did not relapse.

Enrolment was terminated on May 28, 2014, and the data were released to the study committee for analysis. When the study was submitted for monitoring with the dataset from Dec 31, 2015, two (4%) of 49 evaluable patients had an event before 1 year of follow-up. The number of patients without an event in the first year after enrolment (47 [96%] of 49 patients), exceeded the number required to identify the regimen as providing sufficient disease control to warrant further investigation (45 patients). The median follow-up time for all evaluable patients was 42 months (IQR 36–62).

4-year event-free survival was 92% (95% CI 79–97) and 5-year event-free survival was 88% (72–95; figure 2). In post-hoc analyses, 4-year overall survival was 95% (95% CI 82–99) and 5-year overall survival was 91% (75–97; figure 3). Events occurred in a total of five (10%) patients, four of whom had an event less than 15 months from diagnosis, and including three relapses of disease in three patients with Evans surgical stage II disease, and two deaths in patients in clinical remission off protocol therapy, which were judged to be unrelated to disease or protocol treatment. The relapses were one patient with a localised recurrence with small-cell undifferentiated elements and positive annotation factors (P1, V1); one patient without annotation factors and without small-cell undifferentiated elements with a combined localised, nodal, and metastatic recurrence and evidence of preoperative tumour rupture; and one patient with positive annotation factors (P2, V2) and without small-cell undifferentiated elements with a metastatic recurrence. All patients had increased α -fetoprotein at the time of recurrence. Until now, one (2%) patient of the three who relapsed in this cohort has died from disease. We did not collect information about salvage therapies for patients who relapsed. Two (4%) patients died in clinical remission after therapy discontinuation. One patient died of pneumonia and bacterial sepsis 1 year after therapy discontinuation and another patient died of unrelated causes 57 months after therapy completion.

In light of the findings for event-free and overall survival, we did prespecified subgroup analyses according to age, sex, and α -fetoprotein level at diagnosis. There were no detectable differences (data not shown).

PRETEXT group assignments are shown in table 1. Of the 48 patients with available data, 28 (58%) had no proximity to crucial hepatic vasculature. Of the remaining patients who had a resection performed outside of the guidelines, five (10%) tumours had proximity to major hepatic veins but not portal veins, eight (17%) tumours had proximity to major portal veins but not hepatic veins, and seven (15%) had proximity to both major hepatic veins and major portal veins. Three (6%) of the 48 centrally reviewed patients had multifocal tumours.

Four (8%) of eight patients with Evans surgical stage II disease had microscopically positive margins and four (8%) had evidence of tumour rupture (n=2 from the institutional pathologic report and n=2 from the surgical report). The stage II patients included seven patients with PRETEXT II lesions and one patient with PRETEXT III lesions. In a prespecified analysis, five (63%) of the stage II patients had tumours that were in close proximity to the crucial hepatic vasculature, compared with 15 (37%) of the 41 stage I patients (p=0.17).

Resections were all judged grossly complete by the operative surgeon. Operative procedures included right lobectomy (n=23 [47%]), left lobectomy (n=8 [16%]), right lateral segmentectomy (n=7 [14%]), non-anatomic wedge resection (n=6 [12%]), left lateral segmentectomy (n=4 [8%]), and left trisegmentectomy (n=1 [2%]). Surgical complications were noted in two (4%) patients who had bile leaks, both of whom required re-exploration, one of whom also subsequently had a bowel perforation that required a third surgical procedure. A single patient required vascular reconstruction that was not associated with a complication.

Central pathological review confirmed the diagnosis of hepatoblastoma for all patients. Seven (14%) patients had isolated foci (1–10% of tumour) of small-cell undifferentiated elements identified by pathological central review but not by the treating institution. Per protocol, these patients remained eligible for this study group. Only one of these patients with central small-cell undifferentiated elements, the patient described above with the bile leak and bowel perforation and two additional surgeries, has recurred. A detailed analysis of patients with small-cell undifferentiated elements enrolled on all four groups in this study will be reported elsewhere.

Reporting of dose reductions was not specifically mandated for this low-risk stratum. However, deviations from protocol-defined therapy were reported in two (4%) patients, each of whom were not given a single dose of vincristine because of neuropathy (vocal cord paralysis, ileus). No patient discontinued therapy because of toxicity.

As per protocol, grade 1–2 events were not recorded unless they resulted in hospital admission for more than 24 h, and none such events were reported. The most common grade 3–4 adverse event was febrile neutropenia, in seven (14%) patients (table 2). Grade 3 infection and diarrhoea were noted in four (8%) patients each, and three (6%) patients had decreased neutrophil counts. Peripheral neuropathy was noted in two (4%) patients and grade 3 hearing impairment in one (2%) patient. There were no treatment-related deaths.

Discussion

For children who have complete resection at diagnosis, event-free survival after treatment with only two cycles of cisplatin, fluorouracil, and vincristine chemotherapy post-resection had sufficient disease control. These results will affect the care of about a third of patients with newly diagnosed hepatoblastoma and are the third dose reduction study reported for hepatoblastoma by the Children's Oncology Group. A previous report¹² established that resection alone could achieve good outcomes for children with pure fetal histology, affecting about 6% of newly diagnosed patients with hepatoblastoma. These results support the concept that two cycles of chemotherapy produce similar results as four chemotherapy cycles. Furthermore, the surgical guidelines provided in this trial and the results suggest that careful risk stratification and radiological evaluation can identify children with non-metastatic hepatoblastoma who should be considered for upfront tumour resection at the time of diagnosis.

The primary benefit of this strategy is to reduce the acute and long-term toxicities of platinum-based chemotherapy. In particular, increased numbers of chemotherapy cycles are associated with increased ototoxicity.³ These data show the benefits of upfront tumour resection when feasible, and of diminished chemotherapy with decreased long-term morbidity while maintaining curative intent.

Overall survival for all stages of hepatoblastoma has improved significantly with platinum-based chemotherapy, as documented by studies done in the USA, Europe, and Japan.^{4,5,13} The SIOPEL group has reported good outcomes in patients with resectable hepatoblastoma using neoadjuvant chemotherapy before resection, including high frequency of resections and low frequency of surgical complications.¹⁴ These results have led to a worldwide decrease in patients having resection at diagnosis, and initially resulted in slower than expected accrual to this low-risk group of the AHEP0731 trial. Although outcomes in both this study and the SIOPEL study¹⁴ are good, patients in this study received a total of 200 mg/m² of cisplatin, which is less than half the 480 mg/m² that patients with standard-risk disease in the SIOPEL study currently receive. The reduced cumulative chemotherapy dose used in this study achieved comparable overall survival and had resection-related complications similar to those reported by SIOPEL and others.^{2,15}

For low-risk patients, the reality of serious cisplatin-induced ototoxicity^{3,6} has made dose reduction an important goal for oncologists. Sodium thiosulfate neoadjuvant chemotherapy has been explored in the SIOPEL 6 trial (NCT00652132) for patients with standard-risk disease, and initial results suggest no negative effect on overall survival.¹⁶ However, we believe that the best way to ensure the least number of hearing-compromised survivors of hepatoblastoma is to decrease the total cumulative administered dose of cisplatin.

The Children's Oncology Group has used cisplatin, fluorouracil, and vincristine, without doxorubicin, as the standard care for patients with early stage disease for more than two decades.⁴ A recent SIOPEL trial⁶ also showed that doxorubicin is not necessary in standard-risk patients. The use of fluorouracil and vincristine within the cisplatin, fluorouracil, and vincristine regimen has been debated extensively. However, the results observed here and the

observed low toxicity of two cycles of cisplatin, fluorouracil, and vincristine will make it difficult to measure the benefit of elimination of these two drugs in favour of cisplatin monotherapy.

This study has several limitations. It was designed as a single-arm, non-randomised trial because the numbers of potential patients did not make a randomised trial possible. The reported ototoxicity is low for patients treated with two cycles of chemotherapy, but comparison of ototoxicity in children treated in the intermediate-risk group of this study, with higher cumulative doses of cisplatin, will be necessary to document an actual toxicity benefit of the dose reduction. All three disease-related events (disease recurrence) observed in this study group occurred in patients with Evans surgical stage II disease and included patients with surgical complications and extrahepatic extension. Previous data and studies have included the small numbers of the stage II patients along with stage I patients with similar outcomes.³ The small numbers of patients in this study prevent further analysis, but attention to the overall survival of patients with stage II disease in the newly opened Pediatric Hepatic International Tumor Trial (NCT03017326) is warranted. Patients with post-resection microscopic residual disease might be at less risk of recurrence than patients with tumour rupture, contiguous extrahepatic extension, or unresectable major vascular involvement (V and P). The results of this study raise the question of whether closer adherence to the surgical resection guidelines in AHEP0731, which counselled against upfront resection in patients with positive PRETEXT annotation factors, might further improve outcomes. The rarity of paediatric hepatic malignancies results in limited case exposure for paediatric surgeons worldwide. The decision about whether a tumour is initially resectable is partly affected by the experience of the surgeon and their assessment of radiographic studies. To our knowledge, this is the first hepatoblastoma trial that provides specific surgical guidelines to assist in surgical decision making. These guidelines were intended to be permissive rather than restrictive. Because several patients had resections done outside of the guidelines, a detailed analysis of the surgical procedures and correlation with outcomes will be the subject of a more comprehensive analysis of all four risk groups in this study, attempting to determine to what extent PRETEXT groups and annotation factors are predictive of surgical resectability. It remains crucially important that every effort is made to safely perform the correct initial surgical procedure, and to achieve grossly negative margins.

The results here also suggest that future studies might explore chemotherapy reductions in other cohorts of patients with good outcomes. Some patients who do not have resection at diagnosis, but who might become resectable early in their treatment course, could be worth consideration for chemotherapy reduction. However, the results reported herein cannot be definitively extrapolated to the safety and activity of dose reduction for patients with larger tumours treated with neoadjuvant chemotherapy. The recently opened international collaborative trial (Pediatric Hepatic International Tumor Trial), with participation from SIOPEL, Japan, and COG will test the efficacy of two courses of postoperative chemotherapy in patients who can be resected after two cycles of neoadjuvant chemotherapy. Although it is possible that patients with more advanced disease might need more chemotherapy to achieve disease control, equivalent outcomes have traditionally been observed for patients with non-metastatic disease treated over the past several decades,

regardless of the timing of resection.¹ Whether the cohort of patients reported here might be candidates for a further reduction and complete omission of chemotherapy is a question for a future study. Although that hypothesis was considered during the design of this study, it was disregarded as not having sufficient supportive evidence-based data for such an approach.

In summary, minimal adjuvant chemotherapy can achieve long-term disease control in patients with low-risk hepatoblastoma resected at diagnosis. These results of the low-risk stratum of AHEP0731 show that chemotherapy with ototoxic agents can be effectively and safely reduced for these patients. The development of evidence-based surgical guidelines using internationally constructed and accepted criteria based on PRETEXT group and annotation factors will be crucial for the success of this approach to translate into improved outcomes for patients with low-risk disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and all authors had final responsibility for the decision to submit for publication.

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Research in context

Evidence before this study

Paediatric liver cancers are among the most rare pediatric cancers. Therapeutic strategies have been guided by the results of cooperative group clinical trials from North America, Europe, and Asia. We searched PubMed on July 1, 2018, for clinical studies using the search term “hepatoblastoma.” There has been consensus that cisplatin and doxorubicin are the most active chemotherapeutic agents. However, although it is accepted that surgical resection of the primary tumour is the foundation of therapy with curative intent and overall survival is directly related to the degree of resectability, the optimal number of chemotherapy cycles and the timing of surgery has been debated.

Added value of this study

For patients eligible for upfront resection, good overall survival could be maintained with a shorter chemotherapy course. These findings provide new data to be used for optimising therapeutic strategies in determining timing of resection and, potentially, the amount of post-resection chemotherapy required for curative intent.

Implications of all the available evidence

These data suggest that identification of appropriate candidates for upfront surgical resection can result in these patients receiving less chemotherapy, and being at reduced risk of both acute and long-term toxicities. These data might also suggest that patients who have a delayed resection after neoadjuvant chemotherapy might be also candidates for a dose reduction. This concept is being tested in the recently opened Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT) for children with liver tumours.

See **Online** for appendix

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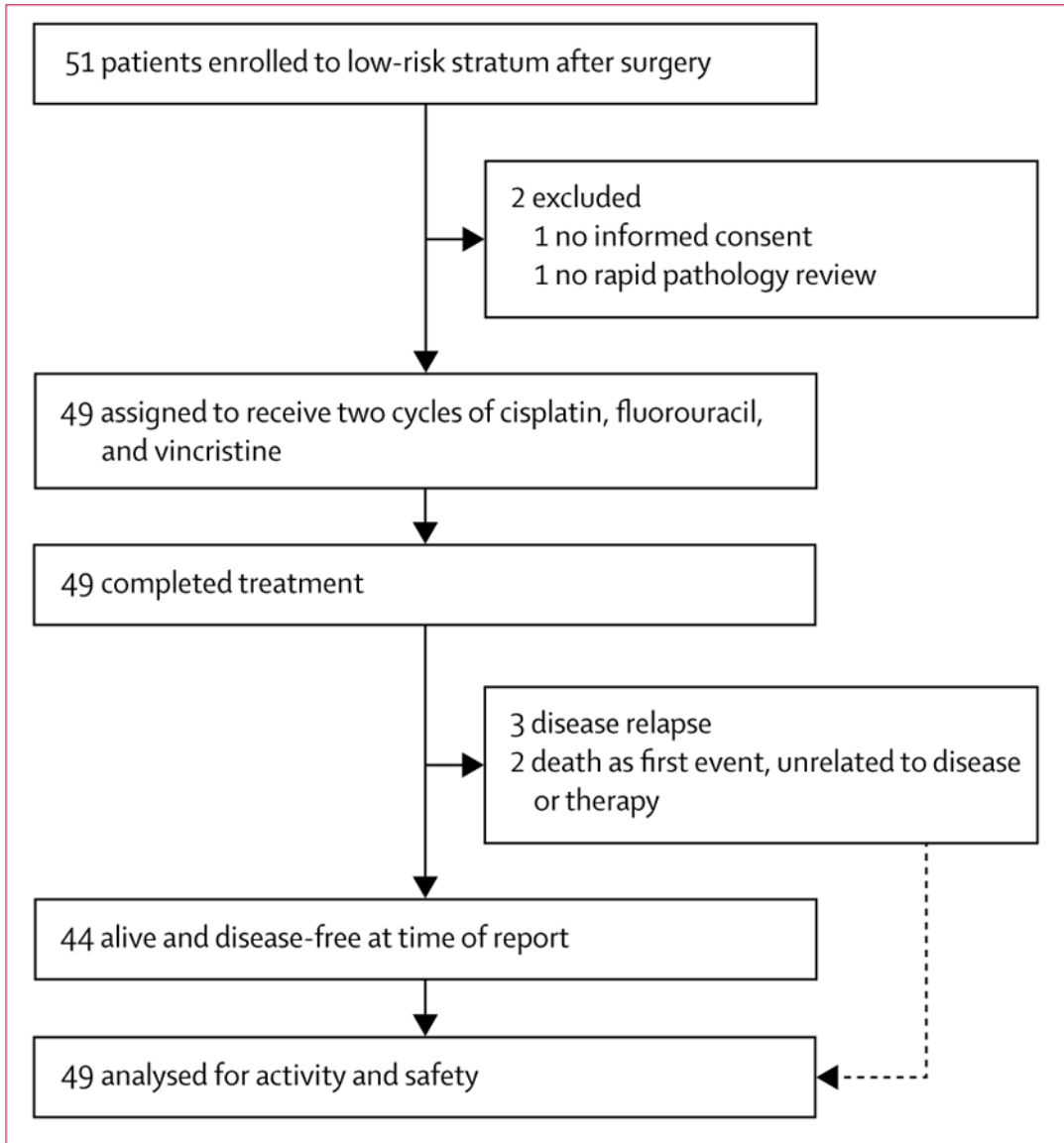


Figure 1. Trial profile for patients enrolled to the low-risk stratum
The complete prespecified trial profile is in the protocol (appendix).

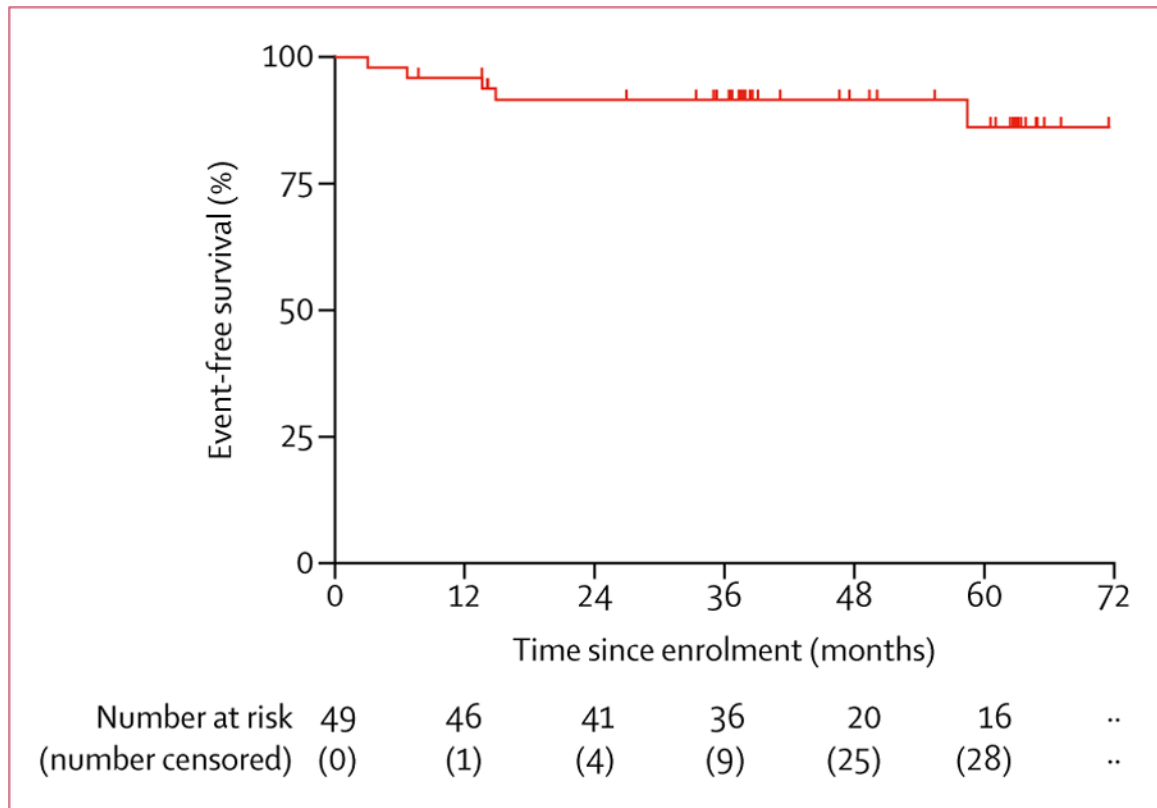


Figure 2.
Event-free survival

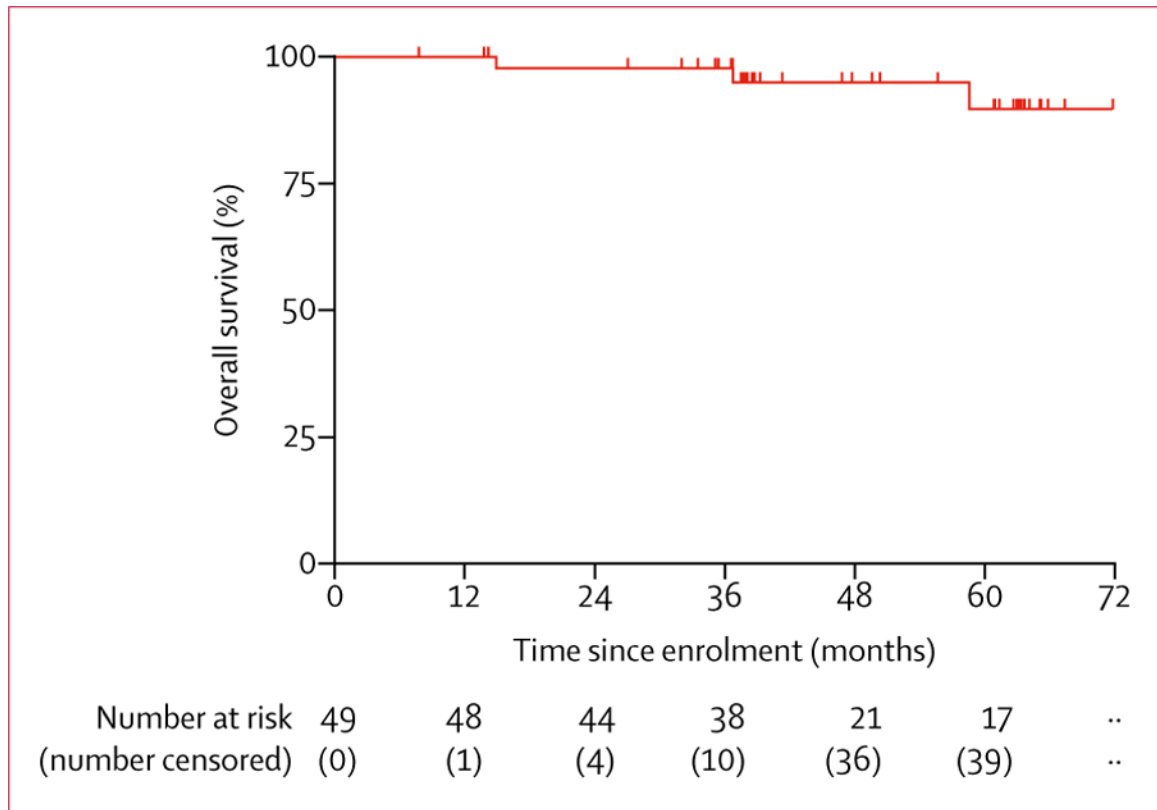


Figure 3. Overall survival
 Overall survival was analysed post hoc.

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Table 1:

Baseline characteristics

	Participants (n=49)
Age	
<12 months	13 (27%)
1–3 years	25 (51%)
3–8 years	11 (22%)
Sex	
Male	35 (71%)
Female	14(29%)
PRETEXT group	
I	7(14%)
P negative	7(14%)
PO	0
PI	0
P2	0
P3	0
V negative	5(10%)
VO	2(4%)
VI	0
V2	0
V3	0
II	39 (80%)
P negative	26 (53%)
PO	4(8%)
PI	5(10%)
P2	4(8%)
P3	0
V negative	30 (61%)
VO	0
VI	3(6%)
V2	5(10%)
V3	1(2%)
III	2(4%)
P negative	0
PO	1(2%)
PI	1(2%)
P2	0
P3	0
V negative	1(2%)
VO	1(2%)
VI	0

	Participants (n=49)
V2	0
V3	0
IV	0
Unknown *	1(2%)
Proximity of tumour to major hepatic vessels	
Portal, both right and left or bifurcation (PO. PI. P2, P3)	48(98%)
P negative	33 (68%)
PO (<1cm)	5 (10%)
PI (touching vessel)	6(12%)
P2 (cSstortion or encasement)	4(8%)
P3 (thrombus in lumen)	0
Unknown *	1(2%)
Major hepatic veins or inferiorvena cava (V0.VLV2.V3)	48(98%)
V negative	36 (74%)
V0(<1 cm)	3(6%)
VI (touching vessel)	3(6%)
V2 (distortion or encasement)	5 (10%)
V3 (thrombus in lumen)	1(2%)
Unknown *	1(2%)
Evans surgical stage	
I	41(84%)
II	8 (16%)
Serum a-fetoprotein level	
100 to <1000 ng/ml	10 (20%)
1000–999999 ng/mL	38 (78%)
Unevaluable	1(2%)

Data are n (%). PRETEXT=Pretreatment Extent of Disease.

* Patient diagnosed prenatally, no postnatal imaging done before surgery. AFP in newborn drawn postoperatively.

Table 2:

Adverse events

	Grade 3	Grade 4
Febrile neutropenia	7 (14%)	0
Infection	4 (8%)	0
Diarrhoea	4 (8%)	0
Hypokalaemia	3 (6%)	1 (2%)
Dehydration	3 (6%)	0
Hyperkalaemia	2 (4%)	0
Hypermagnesaemia	2 (4%)	0
Neuropathy	2 (4%)	0
Neutrophil count decreased	2 (4%)	1 (2%)
Vomiting	2 (4%)	0
Hyperglycaemia	1 (2%)	1 (2%)
Hypernatraemia	1 (2%)	1 (2%)
Anaemia	1 (2%)	0
Anorexia	1 (2%)	0
Apnoea	1 (2%)	0
Hypertension	1 (2%)	0
Hyponatraemia	1 (2%)	0
Mucositis	0	0
Nausea	1 (2%)	0
Ototoxicity	1 (2%)	0
Small intestinal obstruction	1 (2%)	0

As per protocol, grade 1 and 2 toxicities only required reporting if they resulted in hospital admission for more than 24 h, and none were reported. There were no deaths due to adverse events.