RESEARCH BRIEF

Outcomes of Hepatoblastoma in the Indian Context

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A comprehensive review and critical appraisal of published and grey literature was undertaken to identify current treatment practices and outcomes of children with hepatoblastoma in India. Eight single-centre studies with 157 patients (range five to 36 patients in each study) were included. Pre-operative chemotherapy (mainly cisplatin and doxorubicin) followed by surgical resection and additional chemotherapy was the usual practice. There was no stratification of treatment by risk group in any of the studies. The median event-free survival ranged from 33-100%. The two main reasons for treatment failure were treatment-related mortality (0-50%) and progression of disease (0-30%).

Key words: *Hepatoblastoma, India, Outcome, Prognosis, Survival.*

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Hepatoblastoma, the most common malignant childhood liver tumor, has its highest incidence in the first two years of life and shows a male preponderance. The overall 5-years survival of this cancer had improved to 75% at the beginning of the 21st century [1] compared to only 35% in the 1970s [2], by and large using newer chemotherapy strategies [1-3] including a treatment strategy of pre-operative chemotherapy with cisplatin and doxorubicin (PLADO) followed by delayed surgical resection of the tumor.

There is a paucity of published information from India on children with hepatoblastoma. This study aims to assess current treatment outcomes of children with hepatoblastoma in India by a comprehensive review of the published and grey literature.

METHODS

A comprehensive search of Medline, Embase, Web of Science and Scopus databases using keywords "hepatoblastoma" and "India" was done. The search was limited to studies published from 2001 onwards. Additionally, abstracts from annual Congresses of International Society of Paediatric Oncology (SIOP) and American Society for Clinical Oncology (ASCO) for the last 10 years (2001-2010) were hand-searched. Any single or multi-center study from India was eligible for inclusion. If the multi-center study from India was part of an international collaboration, it was included if data specific to the Indian center was available. If there was more than one study from the same institute, only the study from the most recent time period was included. Case reports were excluded. A data extraction form was created and demographic, clinical and outcome data were extracted from the studies identified. Outcomes of interest were survival, mortality, progression of disease and abandonment of treatment.

RESULTS

The initial search identified 226 studies (***Fig.* 1**), of which eight studies (4 published and 4 abstracts from scientific meetings) met the inclusion criteria for this review (**Web Table I**) [4-11].

There were a total of 157 patients (range 5-36 patients in study) with a median age of 12 to 24 months. None of the studies stratified patients for treatment based on stage or risk group. In all the studies, majority of patients (range 67-100%) received pre-operative chemotherapy mainly with PLADO followed by surgical resection (75-100% of patients). The extent of resection was not always specified. Surgery was followed by additional chemotherapy. The main causes of treatment failure were progression of disease (range 0-30%) and treatment related mortality (range 0-50%). The censored (excluding those who abandoned treatment) event-free survival ranged from 33-100% with varying degrees of follow-up. Although the data on treatment from the four published studies were similar to the four abstracts from scientific meetings, the outcomes of the published studies were generally better. Only three studies reported treatment abandonment that ranged from 25% to 62% [6,10,13].

WHAT THIS STUDY ADDS?

- Survival rates for children with hepatoblastoma in India range from 33-100%, with toxicity-related deaths and progression of disease being the main causes of treatment failure.

DISCUSSION

Before drawing conclusions based on the observations in the studies identified in this review, certain caveats need to be considered. Firstly, only a small number of studies have been identified, all of which are single-center, mostly retrospective case-series and some have not been published (hence not peer-reviewed). Secondly, key baseline information like stage of disease at presentation was either not specified or specified by using the American (POG) or European (PRETEXT) classification system, thus limiting an understanding of factors that affect outcomes. Finally, there was variable inclusion and reporting of outcomes on those who refused or abandoned treatment. To allow for comparability, the survival data is presented (***Web Table* I**) after censoring those who abandoned treatment. Despite these caveats, this review allows us to make several important observations.

The treatment-related mortality was mainly due to sepsis, but there were also some peri-operative deaths. There were no deaths due to cardiotoxicity although not all studies gave details of toxicity. In the treatment of hepatoblastoma, myelosuppression caused by chemotherapy and contributing to sepsis can be significant and these toxicity-related deaths may reflect challenges in providing optimal supportive care. Using cisplatin alone for treating standard risk hepatoblastoma (which has been shown to be as effective as PLADO [12]) in a resource-limited setting like India has clear advantages. This would make the treatment less myelosuppressive, potentially leading to a decrease in treatment related morbidity and mortality. Additionally, the treatment is likely to be more cost-effective, which can have a knock-on effect on reducing treatment abandonment [13]. A multi-center pilot study [14] in India is currently underway to study the efficacy and affordability of cisplatin monotherapy and this should provide some answers to the above hypotheses.

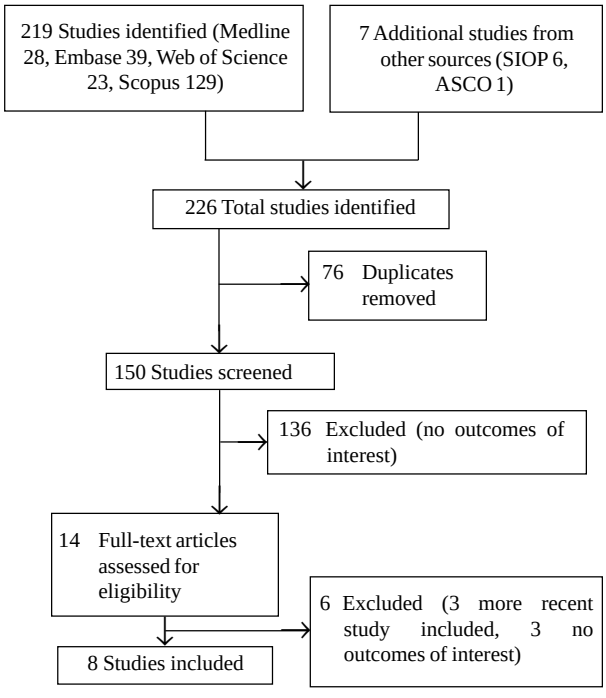

FIG. 1 *Flow diagram of study selection.*

The other reason for treatment failure was progression of disease. It is likely that a greater proportion of those who progressed had high-risk hepatoblastoma at presentation although there was insufficient data in the individual studies to confirm this. Patients with high-risk hepatoblastoma need more intense initial chemotherapy which has to be followed-up by complete hepatectomy and subsequent orthotopic liver transplantation in a proportion of patients [15]. At present, this treatment strategy is not prevalent in India although the first successful liver transplant for hepatoblastoma has been recently reported from the country [16]. While such a strategy of more intense chemotherapy along with better supportive care could improve outcomes, the gains are likely to be modest in the absence of widespread availability of liver transplantation as a therapeutic option.

In addition to treatment and supportive care related factors, stage of disease at presentation has been consistently shown to be related to prognosis [17]. In India, one might anticipate that as a consequence of economic and healthcare infrastructure barriers, there may be delays in presentation that could lead to an advanced stage at presentation and consequently an adverse outcome. From this review, there is little evidence of this promise. Five of the eight studies [6,7,9-11] reported stage of disease at presentation and in all except one [7], this was not different from that reported

from resource-rich nations [1-3]. Future larger multicentre studies from India need to answer this question in a more definitive way.

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