The PLUTO is a registry developed by an international collaboration of the Liver Tumors Strategy Group (SIOPEL) of the SIOP. This registry establishes a multicenter, multi-institutional cooperative database with prospective registration of pediatric patients (<18 yr) who receive a liver transplant for treatment of a primary malignant liver tumor. By reviewing the results to date, we hope we can motivate more centers to participate, enroll patients, complete data entry, and boost the potential impact of the collaborative effort. To achieve this goal, a large number of patients are needed, which requires an intensified international collaboration. Pediatric oncologists, pediatric surgical oncologists, and pediatric liver transplant surgeons are all encouraged to participate and contribute. This is a preliminary glimpse of what we hope to be a series of interim reports over the next decade from the steering committee to help guide therapy in this very challenging group of children.

Abbreviations: COG, Children’s Oncology Group; HB, hepatoblastoma; HCC, hepatocellular carcinoma; HEHE, hepatic epithelioid hemangioendothelioma; IRB, institutional review board; PLUTO, Pediatric Liver Unresectable Tumor Observatory; PRETEXT, PREtreatment EXTent; SIOP, Societe Internationale d’Oncologie Pediatrique.
registry. Specific data regarding chemotherapy and immunosuppression are collected in an attempt to define best practices and possible undesired interactions. Additional variables specifically examined include histologic subtype, vascular invasion (including either gross or microscopic invasion), metastases, and the multifocality, size, and number of nodules of the tumor. This last examination of size and number of nodules will help us determine if the Milan Criteria originally developed for adults with HCC are applicable or appropriate for use in children. Recent data suggest that these Milan criteria require modification for use in children, and the PLUTO outcome data will help us determine an outcome based on an appropriate set of criteria for children (5).

Published results for the most rare tumor types like hemangioendothelioma, embryonal sarcoma, undifferentiated sarcoma, and angiosarcoma are anecdotal at best. A collective registry of outcomes for the most rare tumor types will help set best practice transplant criteria and define outcomes.

Methods

During a meeting in 2004, the SIOPEL group ascertained that the role of liver transplantation in the treatment of primary, malignant liver tumors could not be clarified on the basis of retrospective studies and publications. The creation of an international registry was suggested for the prospective collection of pediatric patients. The first author was entrusted with the task of developing a web site with the technical assistance of CINECA, which is a non-profit National Institute of Oceanography and Experimental Geophysics, the National Research Council, and the Ministry of Education, University and Research. Cineca is located in Bologna, Italy and operates in the technological transfer sector through high-performance scientific computing, the management and development of networks and web-based services, and the development of complex information systems for treating large amounts of data. It offers support to the research activities of the scientific community through supercomputing and its applications. Several work sessions in Bologna, during 2005 and early 2006, were devoted to identification of relevant items, setting up of the datasheets and data entry system at Cineca, and design of the web site (http://pluto.cineca.org). An international steering committee was set up, including representatives of SIOPEL, the COG Liver Tumor Subcommittee, The German Cooperative Pediatric Liver Tumor Study Group, the SPLIT registry, the Italian Association of Pediatric Hematology and Oncology and representatives of Easter Europe, South America, and Asia; consultants were included from radiology and pathology. The design and the content of the web site were discussed and approved by the steering committee. Great attention was paid to the ethical aspects. The project was approved by the Bio-Medical Ethics Committee of the Université Catholique de Louvain, Belgium (home university of the first author). Centers and colleagues willing to contribute were suggested to request an ID and password. The challenge of obtaining approval by the local ethics committee or IRB was the task of individual contributors. PLUTO was launched in 2006 for children <18 yr transplanted from January first onward.

Results

This first interim analysis of the PLUTO data includes patients entered between January 2006 and April 2009. The dataset to date includes registration of 36 centers in 17 countries. Not all registered centers have completed patient data entry because of several reasons including challenges meeting institutional ethics and IRB review processes. Seventeen of the 36 registered centers have enrolled 70 patients. Of the 70 patients, data entry is complete in 52 cases (Table 1). The largest numbers of patients have been enrolled by Buenos Aires (n = 13) and Pittsburgh (n = 11). In this interim analysis, the results are expressed in percentage of available data for each variable as not all patients had a complete dataset. The most compelling observations are as follows: indication for transplant was HB in 70% (n:49), HCC in 23% (n:16), and rare tumor in 7% (hemangioendothelioma = 2; HEHE = 1; embryonal sarcoma = 1; and rhabdoid sarcoma = 1). Age at transplant was ≤ 10 yr in 90%. Age at transplant was 1–10 yr (Fig. 2), with 93% and 7% primary and rescue transplants, respectively. Neoadjuvant chemotherapy was received by 83% of patients and adjuvant chemotherapy by 40%. PRETEXT at diagnosis was downstaged by one group after neoadjuvant chemotherapy in 20% of PRETEXT III tumors (downstaged from a diagnosis PRETEXT III to a post-chemotherapy and pretransplant POST-TEXT II) and 50% of PRETEXT IV tumors (downstaged from a diagnosis PRETEXT IV to a post-chemotherapy and pretransplant POST-TEXT III). Arterial, portal, and biliary complications were reported in 12%, 7%, and 26%, respectively. Kaplan–Meier overall survival estimate at three yr after diagnosis was 87% for HB and 85% for HCC (Figs. 3 and 4). Of four patients who received a rescue transplant for HB,

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<th>Countries contributing to PLUTO as of April 2009</th>
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one is alive and well, one is alive with relapse, one died from relapse, and the outcome of the last patient is unknown. One child who received a rescue transplant for HCC is alive and well. Extrahepatic recurrence occurred in six patients with HB (12.2%); three died and three were alive at last follow-up. Recurrence occurred in four patients with HCC (25%); one died from infection and three were alive at last follow-up. Recurrence occurred in one patient with hemangioendothelioma, alive at last follow-up. In total, five of 49 patients with HB (10%) died (three from recurrence, one from chronic rejection, and one from portal thrombosis). One of 16 patients with HCC died (6%) from infection. Six patients with HB presented with lung metastases (1 PRETEXT III and 5 PRETEXT IV). All cleared their lungs with pretransplant chemotherapy and underwent a successful transplant. One relapsed three months after transplant and died seven months later. The remaining five were alive five, eight, 23, 24, and 25 months post-transplant, at last follow-up. No registered patients have had a pretransplant thoracotomy to resect metastatic tumor.

Discussion

This manuscript presents a preliminary interim analysis of 70 patients enrolled over the first three yr of the registry between January 2006 and April 2009.

This cohort was recruited through international collaboration and remains limited by the inability of more than half of the registered centers to fill all sheets due, partly, to difficulties of completing the necessary approvals for patient

Fig. 1. PLUTO home page.

Patients distribution by age

Fig. 2. Age distribution.
entry and registration. The limited number of patients with completed forms and follow-up restricts the impact of this preliminary study. Epidemiology data, prevalence of HB and HCC, survival rates, and surgical complications are similar to previously published single or multicenter studies. Only five children transplanted for a rare tumor were enrolled; this type of indication, including HEHE (6), remains very controversial; a prospective, international registry will be particularly helpful in this area. Although downstaging after pretransplant chemotherapy was observed in 20% of PRETEXT III and 50% of PRETEXT IV, we may assume that liver transplantation remained indicated because invasion of major venous tributaries precluded a radical resection with conventional surgery. Although follow-up is still short, disease-free survival was observed in five of six patients with HB and lung metastases at presen-

![Kaplan–Meier survival estimate from diagnosis-HB](image)

**Fig. 3.** Kaplan–Meier estimate survival from diagnosis of patients with HB.

![Kaplan–Meier survival estimate from diagnosis-HCC](image)

**Fig. 4.** Kaplan-Meier estimate survival from diagnosis of patients with HCC.
tion, which had cleared after chemotherapy; this is in line with previous observations (7).

Recurrence rate was high in HCC (25%) although three patients remained alive at last follow-up, while one died because of infection; we may expect 100% mortality with further follow-up. Three patients with recurrent HB died, while three more were alive at last follow-up; survival may be expected in some of them if the recurrence responds to chemotherapy. Surprisingly, 17% of patients did not receive neoadjuvant chemotherapy before transplantation, while 60% did not receive chemotherapy posttransplant. This observation underlines the necessity to standardize the chemotherapy in patients needing a transplant, which should follow the same protocols as in children treated by conventional surgery, with the same amount of courses before and after surgery.

The items collected in the PLUTO database will eventually enable us to make a number of specific treatment recommendations once we have achieved a larger recruitment and the database outcome matures. We continue to solicit and encourage collaboration of all pediatric liver transplant centers worldwide. Although participation to date is encouraging, it can and should grow substantially over the next several years. As centers who have volunteered a casual willingness to collaborate begin to see the benefits of such a large collaborative database, these early interim results should help to drive increasing participation. Particularly in the United States, the ethics and IRB process necessary to begin enrolling patients have been a significant roadblock. This challenge is partially addressed as we move into the future by inclusion of the PLUTO IRB process as an integral part of the new COG study of HB. We regret the deficit of collaboration in Asian countries and in some of the largest European countries; this will be a goal for future collaboration and enrollment.

Despite the user-friendly construction of the PLUTO web site, enrolling patients requires motivation based on a common concern about the need to improve the care of children with unresectable primary liver malignancies; the process may appear as time consuming but experience shows that it becomes expeditious when data from a single patient are put together.

The PLUTO data are the asset of centers contributing patients; therefore, they are available to collaborating centers for performing scientific studies that should preferably lead to a publication in a peer-reviewed journal. Regulations for scientific studies and publications have been established (Appendix).

Conclusion

Although the number of patients collected in PLUTO to date is too small to add any analytic power to the existing literature, this new registry has great promise. It has been created to clarify issues regarding the role of liver transplantation in the treatment of children with unresectable liver tumors. By reviewing the results to date, we hope we can motivate more centers to participate, enroll patients, complete data entry, and boost the potential impact of the collaborative effort. To achieve this goal, a large number of patients are needed, which requires an intensified international collaboration. Pediatric oncologists, pediatric surgical oncologists, and pediatric liver transplant surgeons are all encouraged to participate and contribute. This is a preliminary glimpse of what we hope to be a series of interim reports over the next decade from the steering committee to help guide therapy in this very challenging group of children.

Acknowledgments

The professionalism and the efficient collaboration of CINECA (A. Covezzoli, who extracted the data, and M. Derosa) are acknowledged. We are grateful to SIOPEN, IPTA, and Astellas for their support.

Appendix

Regulations for PLUTO-based studies and publications

The PLUTO data are available to scientists/clinicians whose centers regularly contribute to PLUTO. Data can be used to perform scientific studies, which should preferably lead to a publication in a peer-reviewed journal.

Access to the data

To obtain access to the data, a written request should be addressed to the chairperson of the PLUTO Steering Committee serving as custodian of the registry with copy to the chairperson of the SIOPEN group. Decision to release the data should be agreed by both.

The request should contain:

1. Title, objectives, and description of the study
2. Name and affiliation of the investigator(s)
3. Supporting letter by the program director
4. The list of data to be extracted from the PLUTO database
5. A disclosure statement regarding potential conflicts of interest (such as financial affiliations with pharmaceutical companies)

The data will be extracted from the PLUTO database by a collaborator from CINECA.

The statistical analysis will be performed by the investigator and his team; however, it needs to be checked by the SIOPEN group biostatistician.

In case the requested data are not completely available through the PLUTO database, it is allowed to approach
centers contributing patients to PLUTO for additional data. A request to the centers should be cosigned by the investigator and the chairperson of the PLUTO steering committee.

Publications

The results of the study should be submitted to the chairperson of the PLUTO steering committee who will consult with other members of the steering committee, depending on specific issue(s) of the study (e.g., surgical aspects of transplantation, immunosuppression, chemotherapy…).

The investigator will receive the green light for pursuing the writing of the intended oral presentation (and abstract) and/or the publication. The content will be submitted for final approval to the chairperson of the PLUTO steering committee and the other members involved. Full publications only (this rule does not apply to abstracts and oral/poster communications) should be submitted to the SIOPEL Publication Committee before their final release. All centers that have participated in the study will be listed in a footnote or an appendix, mentioning the program director. The contribution of CINECA will be acknowledged. The choice of the journal is made in agreement with the chairperson of the SIOPEL group and the chairperson of the PLUTO steering committee.

Authorship

Authorship of any publication based on PLUTO data (abstract or full paper) is regulated as follows: First and last authorship for those performing the study.

Second and third authorship for the members of the steering committee who have supervised the study. As many authors as possible (this means as allowed by the journal), in general, one per center, according to the number of patients included in the study. After the last author, the statement “for the PLUTO steering committee” should be included, and “for the SIOPEL group,” as well, if appropriate. All centers that have participated with patients in the study will be listed in a footnote or an appendix, mentioning the program director.

References