**Resource Challenged Nations Treatment Guidelines - Synopsis**

**Background**

Hepatoblastoma is a rare tumour, but represents the most common primary malignant tumour of liver in childhood. It accounts for about 1% of all childhood tumours with annual incidence of 1.5 cases per million children. Complete tumour resection is of paramount importance for cure, but operative mortality, without chemotherapy has been reported to be as high. The prognosis for hepatoblastoma has dramatically improved since the introduction in the 1980’s of effective chemotherapy – Cisplatin and Doxorubicin (PLADO) – capable of reducing the tumour volume and making previously unresectable tumours resectable. The operation also becomes safer and easier after pre-operative chemotherapy. Thirdly there is no delay in treating metastatic disease, which is detectable at diagnosis in about 20% of patients.

Society of Pediatric Oncology Liver Cancer (SIOPEL) Group was formed under the auspices of International Society of Paediatric Oncology in 1987 and has gone on to complete three major international collaborative studies in paediatric liver tumours (SIOPEL 1-3).

SIOPEL 1 was the first international clinical trial run by the SIOPEL group and was based on pre-operative chemotherapy using the cisplatin-doxorubicin (PLADO) combination regimen for all patients. The results were encouraging with a 79% 3-yr overall survival (OS) (CI 73-85%) and 67% event-free survival (EFS) (CI 60-75%). The pre-treatment extent of disease was defined by the new PRETEXT classification developed by the group. PRETEXT category proved to be a significant prognostic factor regarding event free and overall survival.

Based on these findings patients in SIOPEL 2 were treated according to extent of disease at diagnosis. ‘Standard risk’ patients, those whose tumour was confined to part of the liver, were treated with Cisplatin alone. The rationale for this was to avoid the risk of cardiomyopathy which may occur many years after treatment with Doxorubicin. Those patients whose tumour involved the whole of the liver or had spread beyond the liver, (‘high risk’) were treated with more intensive chemotherapy, using 3 drugs by adding Carboplatin to the PLADO regimen in an alternating myelotoxic/non-myelotoxic sequence, a regime sometimes referred to as "Super PLADO", in an effort to improve the prognosis.

The short and long term outcome reported from this trial were excellent for ‘standard risk’ patients with an overall response rate of 90%, 97% macroscopically complete resections and a three year overall survival of 91%. This risk stratification was shown to be justified by a striking difference in three year overall survival and event-free survival between the two risk groups.

This finding greatly influenced the design of the third SIOPEL trial (SIOPEL 3). In SIOPEL 3, "standard risk" patients were randomised to receive either PLADO, according to the SIOPEL 1 schedule, or single-agent Cisplatin, according to the "standard risk" SIOPEL 2 regime. The number of "high risk” patients in SIOPEL 2 was insufficient to draw conclusions about any advantage of the Super PLADO regime over standard PLADO, so SIOPEL 3 continued to use Super PLADO as treatment in the "high risk" group. This was later replaced by the SIOPEL 4 protocol, which is more intensified chemotherapy for this group. The results for SIOPEL 3 for ‘standard risk’ patients confirmed that Cisplatin monotherpay is as effective as PLADO in this standard risk group of patients.
The cure rate for standard risk hepatoblastoma reaches promising levels with cisplatin monotherapy and surgery but cisplatin is well known to cause permanent bilateral high frequency hearing loss in a significant proportion of patients. The primary objective of the present SIOPEL trial (SIOPEL 6) is to assess the efficacy of sodium thiosulphate to reduce the hearing impairment caused by cisplatin chemotherapy in children with Standard risk hepatoblastoma.

In summary, the treatment of hepatoblastoma is one of the great success stories for paediatric oncology over the past few decades. We have seen survival rates increase from 25% to over 80% over this period of time. These results have been achieved through effective multidisciplinary team work, advances in surgical techniques and active recruitment of children into successive clinical trials. Patients with hepatoblastoma should be referred to medical centres that have a multidisciplinary team of cancer specialists with experience in treating cancers that occur during childhood.

**Advantages of Cisplatin monotherapy in Resource Challenged Nations.**

Cisplatin and Doxorubicin both have organ threatening side effects. PLADO chemotherapy causes significant myelosuppresion especially in patients from resource challenged nations, where there is already malnourishment and co-existence of other infections (malaria, hepatitis and HIV). Many children could die from febrile neutropenia following PLADO chemotherapy. In addition transfusion of blood products carries substantial risk of infections such as Hepatitis/HIV. Furthermore, there is significant risk of cardiomyopathy in later life following Doxorubicin treatment at a young age. Results of SIOPEL 2 & SIOPEL 3 show that Cisplatin alone is a very effective treatment in patients with Hepatoblastoma. The treatment with Cisplatin monotherapy is not complex, lengthy or especially expensive. Toxicity is mild to moderate with easily manageable complications so most patients are cured at “little cost”. Because all these reasons some instituitions in developing countries may elect to treat all (Standard Risk & High Risk) children with Hepatoblastoma with Cisplatin alone and SIOPEL would endorse this treatment.

Requirements for centres treating these children include: (a) resources for the placement of secure venous access, the measurement of serum alphafetoprotein (AFP) levels and monitoring for the toxicities of Cisplatin, (b) availability of expert liver surgery and (c) the conviction that most children with hepatoblastoma can be cured, so protocols are closely followed. These resources are now available in many "developing countries" one reason for the popularity of the SIOPEL studies internationally.

It is important to adhere to the standard treatment guidelines. The data collected from these initial studies via the SIOPEL RCN registry will then inform and provide the basis for future treatment strategies. The intention would then be to further individualise therapies to suit local conditions acceptable to various countries.

**SIOPEL RCN HEPATOBLASTOMA GUIDELINES**

**Diagnostic procedures.** All children aged less than 16 years with a suspected primary liver tumour should undergo a diagnostic biopsy. The biopsy is mandatory for children aged less than 6 months or over 3 years, or if presenting with a normal serum α-FP level. In case of unequivocal clinical findings (e.g. age between 6 months and 3 years, with a solid hepatic mass, associated with elevated serum
alpha fetoprotein (α-FP) value and maybe with thrombocytosis) the decision about performing the initial, diagnostic surgical biopsy is left to the individual centre. However, biopsy is strongly recommended if there is doubt about the diagnosis. If no biopsy is performed compatible imaging and a raised serum α-FP level (for age) are mandatory for entering patients into the study. No attempt should be made at this time to perform radical tumour removal. At the time of the surgical biopsy, placement of a long-term central venous catheter should be considered.

**Pre-treatment tumour extension evaluation** - At the same time as or soon after the diagnostic procedures an accurate pre-treatment tumour extension evaluation should be performed and a definitive PRETEXT category assigned. All patients should have a lung CT scan to document the presence or absence of metastatic disease and ensure allocation to the correct risk category. In case of discrepancy between chest X-ray and lung CT (i.e. negative chest x ray and positive lung CT, the review panel in India should be consulted for a rapid definitive. Opinion. Subsequently, each patient will be allocated to either ‘Standard’ or ‘High risk’ as indicated.

**First course of chemotherapy** - The entire treatment strategy is based on pre-operative chemotherapy. All patients, regardless of the risk category to which they are allocated, will start therapy with a single dose of CDDP. In the time interval between the first dose of CDDP and the subsequent course of chemotherapy (15 days) central review by a Indian panel of experts of the initial pre-treatment tumour extension findings can take place, if required. The first course of CDDP should be started within 15 days of diagnosis.

**Further treatment** - Additional treatment will depend upon the risk category. 'Standard risk' HB patients will be treated by Cisplatin monotherapy. 'High risk' HB patients will be treated by "PLADO" chemotherapy see Figure 1, SIOPEL RCN study design

**Delayed surgery** - At the end of pre-operative chemotherapy tumour response and the feasibility of definitive tumour resection will be considered. In case of a 'responding' (to chemotherapy) HB which remains unresectable at the end of preoperative chemotherapy, surgery may be postponed until the final two courses of chemotherapy have been delivered pre-operatively.

**Post-operative chemotherapy** - After delayed surgery, all patients will continue with the same chemotherapy as delivered pre-operatively, unless the entire course has already been completed, eg as in the case of a 'slow responder’. For these patients, please contact one of the coordinators.

**NOTES** -
The importance of complete tumour resection **Post** - Only complete tumour resection gives realistic hope of cure for children with HB. Thus, the ultimate goal of the treatment is to aim to achieve a high complete tumour resection rate. This demands that all the available options should be explored before declaring a tumour unresectable. For centres which require assistance in making the final decision on tumour resectability and of the techniques to use, the option of a rapid consultation with a panel of experts (including a liver transplant expert) is available though these guidelines.

Radiotherapy - Radiotherapy has not yet found a definitive role in the treatment of HB.
Figure 1 – RCN STUDY DESIGN

**Standard Risk Patients – CDDP**
Cisplatin (CDDP) 80mg/m² 24 hours IV continuous infusion

**High Risk Patients - PLADO**
Cisplatin (CDDP) 80mg/m² 24 hours IV continuous infusion
Doxorubicin (DOXO) 60mg/m² continuous 48 hours IV continues infusion

Assessment of hearing, kidney function and heart function.

Response evaluation
ROAD MAPS

SIOPEL RCN STUDY for HEPATOBLASTOMA (STANDARD RISK)
Regimen – Cisplatin Monotherapy

Cisplatin (CDDP) 80 mg/m² in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight <10 kg)

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TUMOUR RESPONSE EVALUATION

GFR + Audiogram

DELAYED SURGERY

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END OF TREATMENT

GFR + Audiogram

1 full blood cell count; 2 electrolytes (including Ca++/Mg++); 3 α-fetoprotein
SIOPEL RCN STUDY for HEPATOBLASTOMA (HIGH RISK)
Regimen – PLADO

**Cisplatin (CDDP)** 80 mg/m² in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight <10 kg)

**Doxorubicin (DOXO)** 60mg/m² continuous 48 hours IV continues infusion

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**TUMOUR RESPONSE EVALUATION**

GFR + Audiogram + Echo

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**DELAYED SURGERY**

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