



## *Guidelines for Treating HR HB*

Following closure to recruitment of SIOPEL 4, the SIOPEL group endorse the following guidelines for the treatment of high risk Hepatoblastoma whilst we await completion of SIOPEL 4, full statistical analysis, publication and hopefully clear indication of the best future treatment of children with high risk disease.

The proposed guidelines follow the SIOPEL 3 HR HB regimen of chemotherapy, tumour response and surgery surgery, whilst mindful of the need to monitor long term toxicity.

In the event of any treatment related or surgical queries please refer to the SIOPEL contacts listed within these guidelines.

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## 1 DEFINITION OF HIGH RISK

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'High risk' HB - Tumours involving: (a) all 4 hepatic sections (PRETEXT IV) and/or (b) with evidence of extra-hepatic disease (metastases and/or extra-hepatic abdominal disease).

Lung metastases - All "unequivocal" pulmonary lesions documented on the chest X-Ray **and/or** CT scan considered to be metastatic tumour deposits.

Tumour rupture

Low AFP

## 2 CONFIRMATION OF DISEASE

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**Diagnostic surgical biopsy is strongly recommended for all patients and should be considered mandatory for the following:**

- children under six months of age because of the wide range of possible tumours presenting at this age and the possible confounding effect of a physiologically elevated AFP level because of the age.
- children older than 3 years of age, to distinguish hepatoblastoma from hepatocellular carcinoma;
- all patients with a normal serum AFP.

## 3 GENERAL INDICATIONS FOR SUPPORTIVE THERAPY

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The chemotherapy regimen designed for "high risk" HB is quite intensive and includes the intentional administration of CDDP during the myelotoxic phase, following CARBO/DOXO pulses. The following guidelines must be respected in order to avoid excessive toxicity and to keep to the time schedule of drug administration:

- all children should have a central venous line inserted;
- **If the body weight is less than 10 Kg, drug dosage should be calculated per Kg as indicated in Therapy Modification Section.**
- all children with a body weight equal to or less than the 3rd percentile at the time of starting therapy must have total parenteral nutritional (TPN) support;

In case of renal dysfunction, CARBO actual dosage should be calculated using the modified Calvert's formula after measuring GFR by <sup>51</sup>Cr EDTA or other clearance method. If GFR cannot be measured by clearance method then we would advise the clinician to adapt the dose in function of a calculated estimate of GFR according to the serum creatinine and the child's height and weight. If the GFR is lower than the normal lower limit for age the first dose of CARBO should be reduced by at least 25%. At the clinician's discretion it can then be decreased or increased at subsequent cycles depending on the toxicity profile.

Consider using **Granulocyte colony stimulating factor (G-CSF)** if the first course of CARBO/DOXO has been complicated by severe and protracted neutropenia (regardless of the occurrence of fever) which delayed the institution of the subsequent course of CARBO/DOXO. **G-CSF** is administered subcutaneously at the dosage of 5 mg/kg, 24 hours after the administration of

CDDP; it should be administered until the absolute neutrophil count is  $>500/\text{mm}^3$  for at least two consecutive days. G-CSF must be stopped 48 hours before the next dose of carbo/doxo is given. However, note that G-CSF support is not mandatory in this protocol.

**Pneumocystis carinii prophylaxis** with *trimethoprin-sulfamethoxazole* must be instituted for all patients on 3 days a week - TMP 150 mg/m<sup>2</sup>/d of TMP and SMX-750 mg/m<sup>2</sup>/day (1994 Red Book

- American Academy of Pediatrics);

**Haematologic support** should be provided as needed,

## 4 TREATMENT DESIGN

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**Following diagnosis, all patients will receive pre-operative chemotherapy.** Children classified as having a 'high risk' HB, should be treated with the intensive multi-agent regimen including CARBO, CDDP and DOXO, preceded by a single dose of CDDP

*Pre-operative phase* - Pre-operatively, this regimen will consist of alternating administration of CDDP at days 1, 29, 57 & 85 and of the combination CARBO/DOXO at days 15, 43 & 71. CDDP will be administered regardless of the blood cell count.

Tumour response will be evaluated before days 29, 57 and 85, and just before surgery.

*Delayed surgery* - Delayed surgery should be performed within three weeks of day 85 of the pre-operative chemotherapy. However, if feasible, definitive surgery could be considered also after the second administration of the combination CARBO/DOXO (after day 43). If surgery, is not feasible after the 85th day of the pre-operative phase, but the tumour is responding to chemotherapy, the patient should be treated with, at the most, another 2 doses of CARBO/DOXO alternating with one dose of CDDP. Definitive surgery should be re-considered at the end of these further courses of chemotherapy. All patients should receive at the most 5 courses of CARBO/DOXO and 5 of CDDP alone if the tumour continues to respond to chemotherapy).

*Post-operative chemotherapy* - After delayed surgery patients to receive a further 2 courses of CARBO/DOXO at day 1 and 29 post-surgery alternating with one dose of CDDP at day 15 post-surgery at the same dose and schedule used as for the pre-operative phase.

*Stopping therapy* - The therapy should be stopped after 5 courses of CARBO/DOXO and 5 of CDDP. **Please note:** regardless of the time of delayed surgery all patients should receive the same number of courses and therefore the same total cumulative doses of chemotherapy.

### **Chemotherapy**

**Cisplatin** 80 mg/m<sup>2</sup> over 24 hours as a continuous i.v. infusion on days 1, 29, 57, 85 of the pre operative phase and then after surgery at day 15. **Please, note that Cisplatin should be administered regardless of the peripheral blood cell count.**

**Carboplatin** 500 mg/m<sup>2</sup> as an i.v. infusion from hours 0-1 on days 15, 43, 71 of the pre-operative course; following surgery, as soon as the child has recovered; CARBO will be administered at days 0 and 29. In case of renal dysfunction, the actual dose of CARBO to be administered will be calculated according to the modified Calvert's formula.

$$\text{Dose (mg)} = \text{target AUC (mg/ml.min)} \times [\text{GFR (ml/min)} + (0.36 \times \text{BW (Kg)})]$$

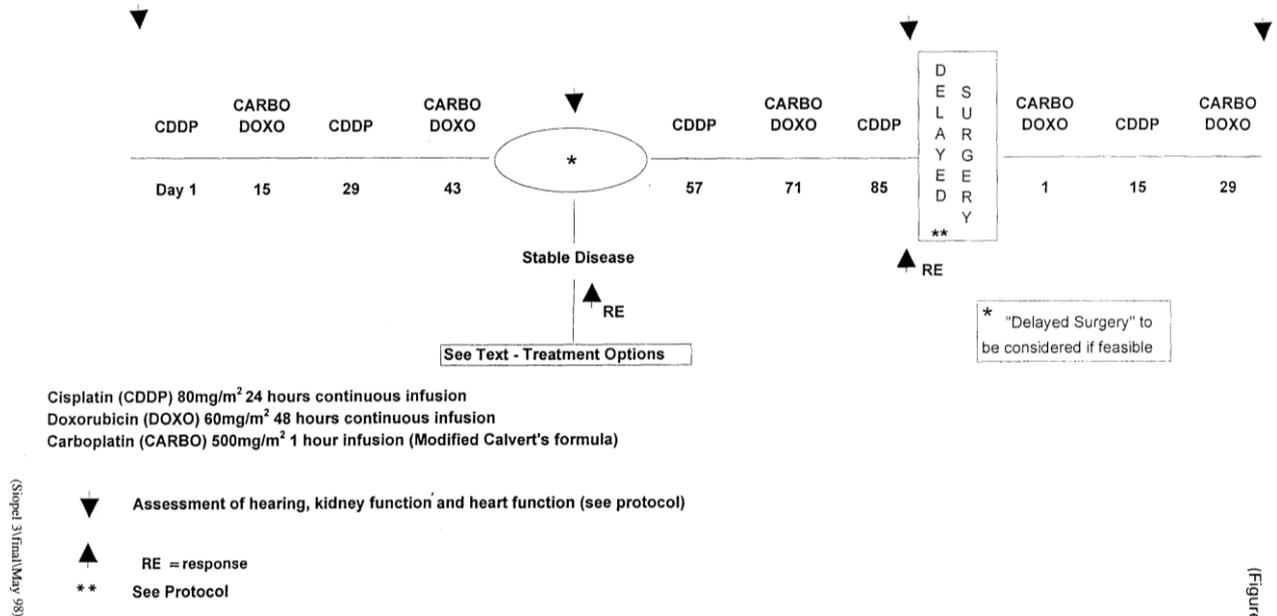
where target AUC is 6.25 mg/mL.min

(AUC = area under the curve)

(BW = body weight)

**Doxorubicin** 60 mg/m<sup>2</sup> as a 48 hours continuous i.v. infusion starting soon after the end of the CARBO infusion at days 15, 43, 71 of the pre-operative course and after surgery, as soon as the child has recovered from surgery at days 1 and 2.

SIOPEL 3 STUDY HIGH RISK HEPATOBLASTOMA PROTOCOL - THERAPEUTIC STRATEGY



## 5 DRUG ADMINISTRATION

### Cisplatin administration

#### Pre-Cisplatin hydration

125 ml/m<sup>2</sup>/hour for 12 consecutive hours of  
 Glucose 2.5%/sodium chloride 0.45% +  
 KCl 10 mmol (10 mEq) /500ml  
 Mg Sulphate 2 mmol (4 mEq) /500 ml  
 CaGluconate 1.5 mmol (3 mEq)/500ml.

#### Cisplatin infusion

- a) Cisplatin 80 mg/m<sup>2</sup> made up to 120 cc with Glucose 2.5%/sodium chloride 0.45% infused at 5 ml/hour for 24 hours , run concurrently with:
- b) 120 ml/m<sup>2</sup>/hour for 24 hours of a solution of  
 Glucose 2.5%/sodium chloride 0.45% +  
 30ml Mannitol 20%/500 ml  
 KCl 10 mmol (10 mEq) /500ml  
 Mg Sulphate 2 mmol (4 mEq) /500 ml  
 CaGluconate 1.5 mmol (3 mEq)/500ml

#### Post-Cisplatin hydration

- a) 125 ml/m<sup>2</sup> /hour for 24 consecutive hours of  
 Glucose 2.5%/sodium chloride 0.45% +  
 KCl 10 mmol (10 mEq) /500ml  
 Mg Sulphate 2 mmol (4 mEq) /500 ml  
 CaGluconate 1.5 mmol (3 mEq)/500ml

A careful record of fluid input and output should be kept. If diuresis falls below 400 ml/m<sup>2</sup> per 6 hrs, furosemide 0.5-1mg/kg intravenously should be given. Careful monitoring of fluid intake and output is essential to prevent renal toxicity and fluid overload. Any fluid lost through vomiting

should be replaced intravenously. Nephrotoxic antibiotics such as Gentamycin should preferably be avoided during and immediately after CDDP infusion. If used, serum levels should be monitored with extreme care.

**Magnesium gluconate**, 3 g/m<sup>2</sup>/day orally, is to be given to all patients, for the entire duration of chemotherapy, beginning with the first cycle.

**Carboplatin** is infused in a 5% glucose solution, 80 ml/m<sup>2</sup>, or 4 ml/kg for infants and children weighing less than 10 kg, over 60 minutes. Immediately after the end of CARBO infusion, start **Doxorubicin** administration. No pre- or post- CARBO infusion hyper-hydration is recommended, but good hydration status is recommended before starting therapy. DOXO is administered in continuous infusion, via a central venous catheter, for 48 consecutive hours. The infusion rate of DOXO should be constant throughout the 48 hour infusion. For this reason infusion of DOXO through a separate i.v. line, in a 5% glucose solution is recommended, using the smallest volume of fluid possible. **If central lines are not available, deep veins should be avoided since extravasation of the drug is dangerous and is not readily appreciated at these sites.** After reconstitution and throughout infusion, all drugs should be protected from the light.

Before each dose of CARBO/DOXO the absolute neutrophil count (ANC) should be greater than 1000/mm<sup>3</sup> and the platelet count greater than 100.000/mm<sup>3</sup>.

CDDP and CARBO are strong emetogenic drugs. Thus, it is recommended to precede the infusions of these two drugs with an anti-emetic cocktail. The 5-HT<sub>3</sub> receptor antagonists are the drugs of first choice.

## 6 THERAPY MODIFICATION

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### By age

**In infants with body weight less than 5 Kg** administer drugs at the following dosages  
Cisplatin 1.7 mg/kg; if well tolerated increase the dose to 2.6 mg/Kg;

This is because for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that 1 m<sup>2</sup> ≡ 30 Kg - and that in very young and small children it is wiser to start with a further 1/3 dose dose reduction.

Carboplatin 11.5 mg/kg; if well tolerated increase the subsequent dose to 16.6 mg/Kg;  
Doxorubicin 1.34 mg/Kg in 48 hours continuous infusion: if well tolerated increase the subsequent dose to 2.0 mg/Kg/48 hours

**For infants and children with body weight between 5 and 10 Kg** administer drugs at the following dosages:

|             |  |
|-------------|--|
| Cisplatin   | 2.6 mg/kg                                      |
| Carboplatin | 16.6 mg/kg                                     |
| Doxorubicin | 1 mg/kg/day x 2 days, ie 2 mg/kg over 48 hours |

This is because for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that 1 m<sup>2</sup> ≡ 30 Kg.

Please, note that infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group (5). Remember also to adjust the amount of hydration fluids according to infant's weight and age.

## 7 RESPONSE AND RELAPSE CRITERIA

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The criteria for judging tumour response are as follows:

- Complete response (CR): no evidence of disease and normal serum AFP value (for age).
- Partial response (PR): any tumour volume shrinkage associated with a decreasing serum AFP value, > 1 log below the original measurement.
- Stable disease (SD): no tumour volume change and no change, or <1 log fall of the serum AFP concentration. N.B. Sometimes the actual volume does not change in response to therapy, but the AFP decreases. These are responses not cases of stable disease.
- Progressive disease (PD): unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration (three successive 1-2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth.

The patient's overall response status is given by the "worst" response for primary tumour and metastases,

eg if primary tumour = PR  
metastases = SD  
then the patient's overall response = SD

Disease-free status/Recurrence Criteria

### ***Disease Free Status***

- a) no evidence of tumour in the liver; (negative hepatic ultrasound and CT scan or MR)
- b) clear chest X-ray (PA and lateral) - if any doubt, do CT scan which must be negative
- c) serum AFP level either normal or compatible with age and/or recent liver resection (in latter case range is up to about 200 ng/ml).

### ***Recurrence***

Biopsy confirmation of recurrence is strongly recommended. However, UNEQUIVOCAL imaging plus unequivocal serial elevation (3 consecutive rising values, taken at weekly intervals) of serum AFP would be an acceptable alternative. If serum AFP is normal, biopsy proof is MANDATORY.

Past experience indicates that an elevated AFP can precede by many weeks the actual documentation of tumour recurrence and that a constantly elevated or rising AFP is always very suggestive of tumour recurrence until proven otherwise.

### **Note**

- Tumour dimensions, especially the primary, MUST be recorded in 3 planes.
- Bear in mind that "no change" or even an increase in "tumour" volume, especially during the first few weeks of chemotherapy, may be the consequence of intra tumoural haemorrhage/oedema. If serum AFP is falling, consider continuing the same chemotherapy for at least one more course.
- Tumour lysis syndrome' may lead to an initial rise in AFP before the level falls.
- To qualify for CR serum AFP must be normal; to qualify for PR there must have been a one log fall of AFP from the initial elevated value. CR or PR is precluded if AFP is rising.

### **For toxicity**

Try to avoid indiscriminate dose-reduction and unnecessary delay of chemotherapy. Give each patient the maximum recommended and tolerable dose of the drugs at the appropriate time.

*Ototoxicity* - The grading system for hearing loss proposed by P R Brock et al will be used in SIOPEL 3 (Careful monitoring of children by an expert audiologist and by serial audiometry

throughout the treatment with CDDP is recommended. To monitor ototoxicity in infants otoacoustic emissions, when available, are a preferable technique to BEAR (brainstem evoked auditory response). Pure tone audiometry is the method of choice in children older than 3 years of age. If a child starts to show signs of high frequency hearing loss he/she should be followed carefully. If grade 3 or 4 ototoxicity is documented, CDDP should be withdrawn.

Grading system for Cisplatin-induced bilateral high-frequency hearing loss

| <i>BILATERAL HEARING LOSS</i> | <i>GRADE</i> | <i>Designation</i> |
|-------------------------------|--------------|--------------------|
| < 40 dB at all frequencies    | 0            | None               |
| > 40 dB at 8,000 Hz only      | 1            | Mild               |
| > 40 dB at 4,000 Hz and above | 2            | Moderate           |
| > 40 dB at 2,000 Hz and above | 3            | Marked             |
| > 40 dB at 1,000 Hz and above | 4            | Severe             |

Data from the literature seem to indicate a possible increase of ototoxicity in patients treated with CARBO and CDDP. Therefore, the hearing should be carefully monitored, (by whatever method is compatible with the child’s age) throughout treatment and thereafter.

*Renal toxicity -*

Glomerular toxicity - Nephrotoxicity of CDDP in children (as in adults) is dose-related and sometimes severe. Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of CDDP-induced renal damage, particularly in children. Careful measurement of Glomerular Filtration Rate (GFR) by isotope clearance is essential for accurate monitoring of renal status. The GFR monitoring in this study will be requested less frequently than previously but it is essential that it be carried out on all patients at the time-points that it is asked for. It should not be done when a child is receiving IV hydration. Please use the same technique on the same child at every time point. Cr<sup>51</sup> EDTA GFR is the preferred technique and involves obtaining the isotope, injecting it into the child and taking 4 blood samples at hourly intervals from an indwelling catheter. It entails less irradiation to the child than daily natural sources. If, for financial reasons this is not available at your hospital, then do a standard endogenous creatinine clearance with a 24 hr urine collection. If the urine collection is not complete, then please repeat it. In cases of severe reduction in <sup>51</sup>CrEDTA GFR (<60 ml/min/1.73 m<sup>2</sup>), discontinue CDDP.

In infants refer to the GFR graph according to age and if the GFR falls below 2 SD below the expected GFR, then discontinue CDDP.

Tubular toxicity - Renal loss of Magnesium and consequent Hypomagnesemia is expected in nearly all children on this study and oral Magnesium supplementation is recommended for all children following these guidelines. Hypomagnesemia is not a reason to stop CDDP. Children can develop other manifestations of renal tubulopathy at the same time as the GFR is improving. Thus, careful monitoring of electrolytes is essential in all children exposed to CDDP treatment. Hypomagnesemia may persist years after stopping therapy.

Infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group. However, CDDP seems no more nephrotoxic in infants than in older children.

Bone marrow toxicity - An absolute neutrophil count (ANC) greater than 1000/mm<sup>3</sup> and a platelet count greater than 100.000/mm<sup>3</sup> are necessary before starting chemotherapy with Carboplatin and Doxorubicin. It is better to delay slightly the institution of chemotherapy until these criteria are met, rather than decreasing the dose. If a delay of one or more additional weeks is required, decrease dosage by 25% for the next course only, and use GCSF.

If a course of chemotherapy results in severe neutropenia ( $ANC < 500/mm^3$ ) associated with fever and sepsis or severe infection and/or severe thrombocytopenia ( $< 10.000/mm^3$  lasting more than 5 days) associated with bleeding, decrease dosage by 25% for the next course. If the subsequent course is not complicated by those events resume the full dosage of the drugs.

*Hepatic toxicity* - No standardised criteria exist for the adjustment of DOXO dosage in the presence of hepatic dysfunction. It seems reasonable to recommend a 50% reduction of DOXO dosage if total serum bilirubin concentration is  $> 3 \text{ mg}/100 \text{ ml}$ , and/or if serum liver enzymes (AST, ALT) are  $>5$  times the normal value. NB Since DOXO hepatotoxicity is actually very rare, elevated AST, ALT should lead to an energetic search for other causes of liver dysfunction, eg viral hepatitis. Neither CARBO nor CDDP doses need to be modified.

*Cardiotoxicity* - Regular monitoring for possible cardiotoxicity is essential. (The recommended investigation is 2D and M mode echocardiogram, with measurement of shortening fraction (SF). Echocardiogram should be performed when the patient is normothermic, has a normal haemoglobin, and is not being hyperhydrated. True baseline measurements should be obtained prior to administration of DOXO to provide a meaningful reference for comparison with future tests.

**An echocardiogram must be performed prior to surgery.**

Significant deterioration in function is indicated by a shortening fraction  $< 29\%$ . In this event, temporarily withdraw DOXO. If subsequent testing shows an improvement in shortening fraction, consider reintroducing doxorubicin.

A fall in shortening fraction by an absolute value of  $> 10$  percentile units but with an actual SF value  $> 29\%$  (eg SF 42%  $\rightarrow$  SF 31%) may also represent a significant deterioration in function.

## 8 SURGICAL RESECTION

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The ultimate goal of hepatoblastoma treatment is to achieve complete surgical resection of all tumour lesions (both of the primary tumour and the metastases) that remain visible after pre-operative chemotherapy. Only complete tumour resection gives realistic hope of cure for children with hepatoblastoma. This implies that all options should be explored before declaring a tumour unresectable. In this regard, for selected cases, liver transplantation and pulmonary metastectomy must be considered a real option. **See committee contacts for further advice, if required.**

- The surgical team, including the anaesthetist, should ideally have extensive experience in paediatric liver surgery;
- Advanced modern equipment for liver surgery should be readily available;
- Facilities for post-operative intensive care should be optimal;
- The nutritional status of the patient should be evaluated and improved if necessary.

As stated above, the aim of definitive surgery is the microscopical complete (margins free of tumour) resection of the tumour. This means that if, during the operation, the surgeon has any doubts about being microscopically radical, frozen sections of the resection margins should be obtained before proceeding. If positive, the surgeon should try, as long as it is reasonable and possible, to achieve a resection whose margins are tumour free. Thus the final judgement of the surgical act (if macro or microscopically complete) will depend upon the final pathology report.

If there is still evidence of non responding disease and/or persistently elevated serum AFP level at the scheduled end of therapy, alternative therapy should be considered. **Please, contact a SIOPEL committee member.**

**Note** that a persistently elevated serum AFP level usually indicates persistence of active disease until otherwise proven. It is not uncommon to find a slowly rising AFP level, particularly for AFP

level < 100 ng/ml, before actual residual tumour can be identified. In this case abdominal and chest radiological investigations should be repeated until the site of relapse is identified. Occasionally the AFP level eventually declines spontaneously to normal, no cause having been identified.

## 9 SIOPEL CONTACTS

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## 10 ROAD MAP FOR 'HIGH RISK' HEPATOBLASTOMA

**Carboplatin (CARBO)** 500 mg/m<sup>2</sup> 1 hour infusion (16.67 mg/kg if body weight less than 10 kg).

**Doxorubicin (DOXO)** 60 mg/m<sup>2</sup> in 48 hours continuous infusion (2.0 mg/kg if body weight less than 10 kg).

**Cisplatin (CDDP)** 80 mg/m<sup>2</sup> in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight less than 10 kg).

\*See protocol for dose modification by age and weight.

| Day | Actual date | CARBO | DOXO | CDDP | G-CSF | Investigations before instituting therapy     |
|-----|-------------|-------|------|------|-------|---|
| 1   |             |       | -    | X    |       | 1,2,3, GFR, Audio, Echo                       |
| 15  |             | X     | X    |      |       | 1,2, 3  |
| 16  |             |       | X    |      |       |   |
| 29  |             |       |      | X    |       | 1,2, 3  |
| 30  |             |       |      |      | X*    |   |
| 43  |             | X     | X    |      |       | 1,2, 3  |
| 44  |             |       | X    |      |       |   |
| 50  |             |       |      |      |       | <b>Preliminary tumour response evaluation</b> |
| 57  |             |       |      | X    |       | 1,2, 3  |
| 58  |             |       |      |      | X*    |   |
| 71  |             | X     | X    |      |       | 1,2, 3  |
| 72  |             |       | X    |      |       |   |
| 85  |             |       |      | X    |       | 1,2, 3  |
| 86  |             |       |      |      | X*    |   |

### TUMOUR RESPONSE EVALUATION, GFR, AUDIOGRAM AND ECHOCARDIOGRAM DELAYED SURGERY

| Day | Actual date | CARBO | DOXO | CDDP | G-CSF | Investigations before instituting therapy |
|-----|-------------|-------|------|------|-------|---|
| 1   |             | X     | X    |      |       | 1,2, 3                                    |
| 2   |             |       | X    |      |       |   |
| 15  |             |       |      | X    |       | 1,2, 3                                    |
| 16  |             |       |      |      | X*    |   |
| 29  |             | X     | X    |      |       | 1,2, 3                                    |
| 30  |             |       | X    |      |       |   |

### END OF TREATMENT - GFR + AUDIOGRAM + ECHOCARDIOGRAM

\* If the first course of CARBO has been complicated by severe and protracted neutropenia (regardless of the occurrence of fever) which delayed the institution of the subsequent course of CARBO. **G-CSF** is administered subcutaneously at the dosage of 5 mg/kg, 24 hours after the administration of CDDP; it must be administered until the absolute neutrophil count is >500mm<sup>3</sup> for at least two consecutive days.

1 full blood cell count; 2 electrolytes (including Ca<sup>++</sup>/Mg<sup>++</sup>); 3 α-fetoprotein

## 11 GFR

| <b>Age (Sex)</b>  | <b>Mean GFR <math>\pm</math> SD<br/>(mL/min/1.73m<sup>2</sup>)</b> |
|---|--|
| <b>1 week<br/>(males and females)</b>   | <b>40.6 <math>\pm</math> 14.8</b>                                  |
| <b>2-8 weeks<br/>(males and females)</b>  | <b>65.8 <math>\pm</math> 24.8</b>                                  |
| <b>&gt; 8 weeks<br/>(males and females)</b>   | <b>95.7 <math>\pm</math> 21.7</b>                                  |
| <b>2-12 years<br/>(males and females)</b>   | <b>133.0 <math>\pm</math> 27.0</b>                                 |
| <b>13-21 years (males)</b>  | <b>140.0 <math>\pm</math> 30.0</b>                                 |
| <b>13-21 years (females)</b>  | <b>126.0 <math>\pm</math> 22.0</b>                                 |
| Abbreviation: SD, standard deviation  |  |
| <a href="http://www.kidney.org/professionals">http://www.kidney.org/professionals</a> |  |

## 12 AFP VALUES BY AGE

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| <b>AGE</b>       | <b>NO.</b> | <b>MEAN ± S. D. (ng/ml)</b> |   |        |
|------------------|------------|-----------------------------|---|--------|
| Premature        | 11         | 134,734                     | - | 41,444 |
| Newborn          | 55         | 48,406                      | - | 34,718 |
| Newborn -2 weeks | 16         | 33,113                      | - | 32,503 |
| 2 wk -1 month    | 43         | 9,452                       | - | 12,610 |
| 1 month          | 12         | 2,654                       | - | 3,080  |
| 2 months         | 40         | 323                         | - | 278    |
| 3 months         | 5          | 88                          | - | 87     |
| 4 months         | 31         | 74                          | - | 56     |
| 5 months         | 6          | 46.5                        | - | 19     |
| 6 months         | 9          | 12.5                        | - | 9.8    |
| 7 months         | 5          | 9.7                         | - | 7.1    |
| 8 months         | 3          | 8.5                         | - | 5.5    |
| > 8 months       | -          | 8.5                         | - | 5.5    |

From: Book and Sudar Serum AFetoprotein (AFP) Levels in Normal Infants  
Paediatric Research 15 50-52 (1981)