

# 高雄榮民總醫院 神經母細胞瘤診療原則

2020年02月27日第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

# 修訂指引

- 本共識依下列參考資料制定版本
  - 台灣兒童癌症研究群(TPOG)
  - TPOG N2002

# 會議討論

上次會議：2019/02/26

## 本共識與上一版的差異

上一版	新版
1. 依據TPOG N2002版本修訂神經母細胞瘤診療指引。	1. TPOG N2002無新增或修改Protocol，故今年僅審視未修。

# 兒癌-Neuroblastoma

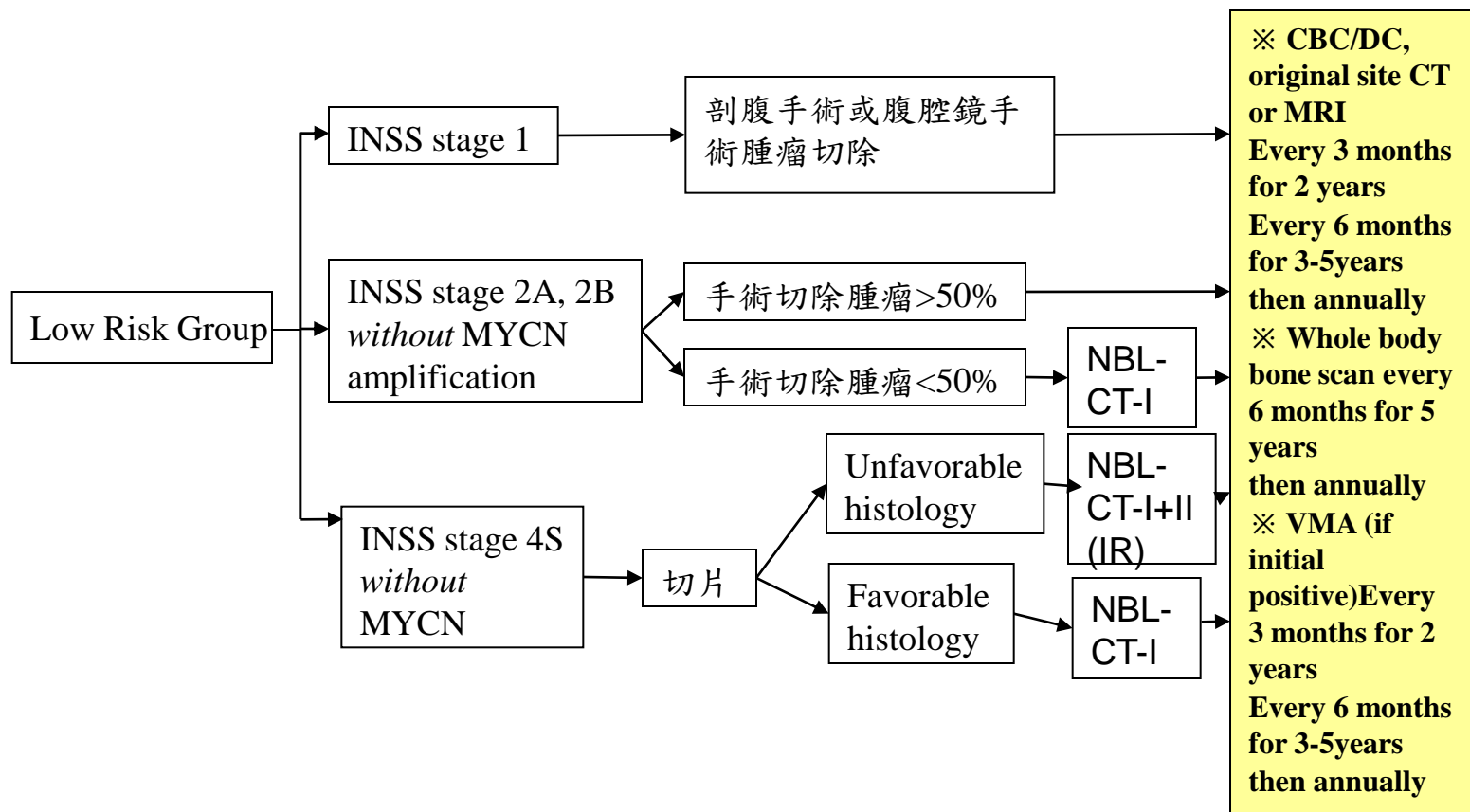
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評估	診斷	治療	追蹤
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- 病史，理學檢查
- 營養及日常體能狀態
- 身高體重，體表面積計算
- 血液常規
- 電解質及肝腎功能
- 凝血功能
- 腫瘤指標 (LDH, ferritin, 24hrs urine VMA)
- 心臟超音波檢查
- 腹部超音波
- 聽力檢查
- 骨髓抹片/切片檢查\*
- 骨頭掃描\*
- 胸腹部電腦斷層攝影 (CT)\* or 核磁共振檢查 (MRI)\* (擇一)
- 腫瘤之N-myc檢測(外送國家衛生研究院)\*

\*與癌症期別相關之主要檢查



★詳見 [APPENDIX I: International Neuroblastoma Staging System \(INSS\)](#)  
★ [APPENDIX II: Assignment of Risk Group Protocol](#)

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## TREATMENT ASSIGNMENT

1. Primary surgical therapy: NBL-LR without risk factors
2. NBL-CT-I: NBL-LR with risk factors
  - ◎Symptomatic patients needed chemotherapy NBL-CT-I
    - Respiratory distress
    - Spinal cord compromise with or without neurologic deficit
    - IVC compression with renal or bowel ischemia
    - Intractable vomiting due to GI obstruction
    - GU obstruction
    - Coagulopathy
  - ◎Patients with intradural extension and emergent paresis: Chemotherapy can be administered prior to biopsy as long as biopsy is performed within 96 hours.
  - ◎Biologically low risk patients in whom < 50% of tumor has been resected should be treated with chemotherapy.
3. NBL-CT-I plus NBL-CT-II: NBL-IR
4. TPOG-N2002-HR: NBL-HR1, NBL-HR2, or NBL-Rel

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## CHEMOTHERAPY PROTOCOL

Baktar prophylaxis 1/4#, 1/2#, 1#, 1 1/2# BID 3 consecutive days a week for BSA < 0.3, 0.3-0.79, 0.8-1.39, 1.4-1.84 m<sup>2</sup> respectively.

Chemotherapy doses are adjusted for children less than 365 days of age or who are  $\leq$  12 kg in weight, and are given in parenthesis below.

(Note) Organ function should be adequate (except those abnormal due to neuroblastoma): Serum creatinine < 1.5x normal; Bilirubin < 1.5x normal; AST/ALT < 2.5x normal; Shortening fraction of > 27% by echocardiography.



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## 化學治療處方建議表: NBL-CT-I

### Chemotherapy

\* For children less than 365 days of age or who are  $\leq$  12kg in weight

#### Cycle 1 (Carboplatin/Etoposide)

##### Day 0

Hour 0: Carboplatin 560mg/m<sup>2</sup> (18mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 1: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S for 2 hours  
(maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 3: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

##### Day 1&2

Hour 0: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S for 2 hours  
(maximum concentration 0.4mg/ml) IVD for 2 hours

#### Cycle 2 (Carboplatin/Cyclophosphamide/Doxorubicin)

##### Day 0

Hour 0: Carboplatin 560mg/m<sup>2</sup> (18mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 1: Cyclophosphamide 1000mg/m<sup>2</sup> (33mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 2: Doxorubicin 30mg/m<sup>2</sup> (1mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 3: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 3 hours

**Note:** Patients with Stage 4S disease may discontinue chemotherapy after 2 cycles or receive one or two additional cycles.

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## 化學治療處方建議表:NBL-CT-I (con.)

### Chemotherapy

\* For children less than 365 days of age or who are  $\leq$  12kg in weight

#### Cycle 3 (Cyclophosphamide/Etoposide)

##### Day 0

Hour 0: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

Hour 2: Cyclophosphamide 1000mg/m<sup>2</sup> (33mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 3: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

Hour 5: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

##### Day 1&2

Hour 0: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

#### Cycle 4 (Carboplatin/Etoposide/Doxorubicin)

##### Day 0

Hour 0: Carboplatin 560mg/m<sup>2</sup> (18mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 1: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours(maximum concentration 0.4mg/ml)

Hour 3: Doxorubicin 30mg/m<sup>2</sup> (1mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 4: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

##### Day 1&2

Hour 0: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours(maximum concentration 0.4mg/ml)

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## 化學治療處方建議表:NBL-CT-II

### Chemotherapy

\* For children less than 365 days of age or who are  $\leq$  12kg in weight

#### Cycle 5 (Cyclophosphamide/Etoposide)

##### Day 0

Hour 0: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

Hour 2: Cyclophosphamide 1000mg/m<sup>2</sup> (33mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 3: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

Hour 5: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 2 hours

##### Day 1&2

Hour 0: Etoposide 120mg/m<sup>2</sup> (4mg/kg)\* in 300 ml/m<sup>2</sup> 2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

#### Cycle 6 (Carboplatin/Cyclophosphamide/Doxorubicin)

##### Day 0

Hour 0: Carboplatin 560mg/m<sup>2</sup> (18mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 1: Cyclophosphamide 1000mg/m<sup>2</sup> (33mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 2: Doxorubicin 30mg/m<sup>2</sup> (1mg/kg)\* in 125 ml/m<sup>2</sup> 2.5% G/S IVD for 1 hour

Hour 3: 2.5% G/S at 125 ml/m<sup>2</sup> /hr IVD for 3 hours

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## 化學治療處方建議表：NBL-CT-II (con.)

### Chemotherapy

\* For children less than 365 days of age or who are  $\leq$  12kg in weight

#### Cycle 7 (Carboplatin/Etoposide)

##### Day 0

Hour 0: Carboplatin  $560\text{mg}/\text{m}^2$  ( $18\text{mg}/\text{kg}$ )\* in 125 ml/ $\text{m}^2$  2.5% G/S IVD for 1 hour

Hour 1: Etoposide  $120\text{mg}/\text{m}^2$  ( $4\text{mg}/\text{kg}$ )\* in 300 ml/ $\text{m}^2$  2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

Hour 3: 2.5% G/S at 125 ml/ $\text{m}^2$  /hr IVD for 2 hours

##### Day 1&2

Hour 0: Etoposide  $120\text{mg}/\text{m}^2$  ( $4\text{mg}/\text{kg}$ )\* in 300 ml/ $\text{m}^2$  2.5% G/S IVD for 2 hours (maximum concentration 0.4mg/ml)

#### Cycle 8 (Cyclophosphamide/Doxorubicin)

Hour 0: 2.5% G/S at 125 ml/ $\text{m}^2$  /hr IVD for 2 hours

Hour 2: Cyclophosphamide  $1000\text{mg}/\text{m}^2$  ( $33\text{mg}/\text{kg}$ )\* in 125 ml/ $\text{m}^2$  2.5% G/S IVD for 1 hour

Hour 3: Doxorubicin  $30\text{mg}/\text{m}^2$  ( $1\text{mg}/\text{kg}$ )\* in 125 ml/ $\text{m}^2$  2.5% G/S IVD for 1 hour

Hour4: 2.5% G/S at 125 ml/ $\text{m}^2$  /hr IVD for 3 hours

**Note:** At the conclusion of 8 cycles, patients shall undergo surgery to the primary site on day 168 or when ANC > 1,000/ $\mu\text{l}$  and platelet > 100,000/ $\mu\text{l}$  for those not in CR.

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## 化學治療處方建議表：N2002-HR1 flowchart

Day 1-7 Cy, Day 8 DDP, Day 10 Ep

Cy Cyclophosphamide 150 mg/m<sup>2</sup> IV or PO QD X 7 days

Day 22-28 Cy, Day 29-31 VP

DDP Pre-Hydrate with normal saline 10 ml/kg over 1 hour.

Day 43-49 Cy, Day 50 DDP, Day 52 Ep

Anti-emetics (e.g. Zofran 0.15 mg/kg 30 min before chemotherapy, then q8h)

Day 72 DDP, Day 73-75 VP

Mannitol 8 g/m<sup>2</sup>/ IV over 15 minutes

Day 92-98 Cy, Day 99 DDP, Day 101 Ep

Cisplatin 90 mg/m<sup>2</sup>/day in 400 ml/m<sup>2</sup> half saline over 2 hours

Day 120-126 Cy, Day 127-129 VP

Hydration with D5W0.45% NaCl + 30 mEq/L KCl + 500 mg/L

Surgery

MgSO<sub>4</sub> + 250 mg/L Ca gluconate at 200 ml/m<sup>2</sup>/hr for 6 hours  
plus 20% Mannitol at 35 ml/m<sup>2</sup>/hr (7 gm/m<sup>2</sup>/hr) IV for 6 hours

After wound healing

Day 1-7 Cy, Day 8 Ep

Hydration with D5W0.45% NaCl + 30 mEq/L KCl at 125 ml/m<sup>2</sup>/hr

Day 21 DDP, Day 22-24 VP

Day 41-47 Cy, Day 48 Ep

Ep Epirubicin 35 mg/m<sup>2</sup> IVP

Day 60 DDP, Day 61-63 VP

VP Etoposide 225 mg/m<sup>2</sup>/day in 500 ml/m<sup>2</sup> normal saline over 2 hrs X 3 days

R/T 3500 cGy

Hydration with D5W0.45% NaCl + 30 mEq/L KCl at 125 ml/m<sup>2</sup>/hr

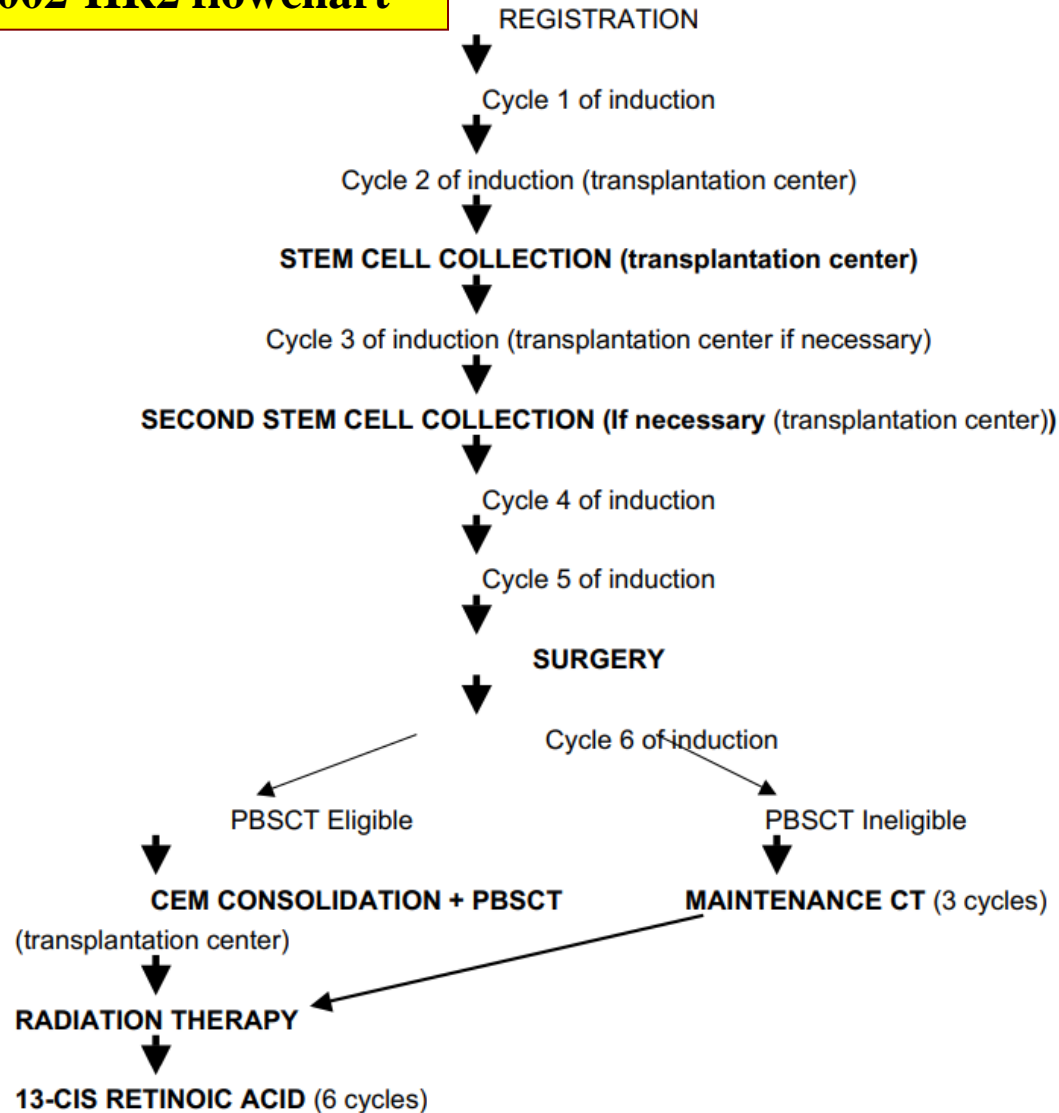
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## 化學治療處方建議表：N2002-HR2 flowchart



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化學治療處方建議表: N2002-HR2 (con.)

## Chemotherapy

Cycle 1, 2, 4, 6 of induction: CDV

### Day 0&1

Cyclophosphamide 2100mg/m<sup>2</sup> (70mg/kg)\* for 6 hours

Oncovin# 0.67mg/m<sup>2</sup> for 24 hours

Adrimycin 25mg/m<sup>2</sup> (0.83mg/kg)\* for 24 hours

### Day 2

Oncovin# 0.67mg/m<sup>2</sup> for 24 hours

Adrimycin 25mg/m<sup>2</sup> (0.83mg/kg)\* for 24 hours

\* For children less than 365 days of age or who are  
≤ 12kg in weight

# 0.022mg/kg if < 12kg, 0.017mg/kg if < 12 months

Cycle 3, 5 of induction: CiE

### Day 0, 1&2

Etoposide 200mg/m<sup>2</sup> (6.67mg/kg)\* for 2 hours

Cisplatin 50mg/m<sup>2</sup>(1.66mg/kg)\* for 1 hour

### Day 3

Cisplatin 50mg/m<sup>2</sup>(1.66mg/kg)\* for 1 hour

\* For children less than 365 days of age or who are  
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## 化學治療處方建議表:N2002-HR2 (con.)

### Chemotherapy

#### Chemotherapy Consolidation+PBSCT

#### Day -7 to -5

Carboplatin  $425\text{mg}/\text{m}^2$  ( $14.2\text{mg}/\text{kg}$ )\* for 24 hours

Etoposide  $338\text{mg}/\text{m}^2$  ( $11.3\text{mg}/\text{kg}$ )\* for 24 hours

Melphalan  $70\text{mg}/\text{m}^2$  ( $2.3\text{mg}/\text{kg}$ )\* bolus

#### Day -4

Carboplatin  $425\text{mg}/\text{m}^2$  ( $14.2\text{mg}/\text{kg}$ )\* for 24 hours

Etoposide  $338\text{mg}/\text{m}^2$  ( $11.3\text{mg}/\text{kg}$ )\* for 24 hours

#### Day -3 to -1 Rest

#### Day 0

Stem cell infusion

#### 13-cis-Retinoic Acid therapy

13-cis-RA  $160\text{mg}/\text{m}^2/\text{day}$  ( $5.33\text{mg}/\text{kg}/\text{day}$ )\* for BID, for 14 days, followed by 14 days rest per cycle

\* For children less than 365 days of age or who are  $\leq 12\text{kg}$  in weight



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化學治療處方建議表:N2002-HR2 (con.)

## Chemotherapy with *abnormal renal function*( $Ccr < 100ml/min/1.73m^2$ )

**Carboplatin** using modified Calvert formula or 10mg/kg if  $\leq 12kg$

$$\text{total dose (mg/day)} = (\text{CCR} \times \text{BSA}/1.73 + 15 \times \text{BSA}) \times 4.1$$

**Etoposide** 200mg/m<sup>2</sup>(6.7mg/kg)\*4 for 24 hours

**Melphalan** 60mg/m<sup>2</sup>(2mg/kg)\* 3

\* For children less than 365 days of age or who are  $\leq 12kg$  in weight

## SURGERY GUIDES

1. Specify initial as well as subsequent operative procedures.
2. The goal of surgery is to provide diagnostic material at diagnosis (biopsy), to accurately stage disease through sampling of non-adherent lymph nodes, and to attempt maximal safe resection either at diagnosis or after chemotherapy (second-look procedure).
3. The lymph nodes should be sampled include all grossly visible regional lymph nodes (identifying contiguous vs non-contiguous), cervical chain (for cervical tumors), paraspinal and mediastinal chains (for thoracic tumors), immediate para-aortic drainage level and area of bifurcation of the aorta, paracaval, interaortocaval (for abdominal tumors), both iliac chains and para-aortic, bifurcation of the aorta, paracaval (for pelvic tumors).
4. For patients of NBL-HR, removal of residual primary tumor and/or other bulk tumor should be attempted after indicated cycles of induction therapy, once the ANC is  $>500/\text{mm}^3$  and the platelet count  $>75,000/\text{mm}^3$  and patients not progressing. If the tumor cannot be resected, ascertain the anatomic reason for unresectability. The application of radiotherapy will be limited to indications described in the following sections.

## RADIOTHERAPY GUIDES -1

### 1. Indication :

- ◆ Symptomatic NBL-LR patients (defined in III) that have not responded rapidly enough to chemotherapy.
- ◆ Viable residual disease after completion of chemotherapy and“second look” surgery.
- ◆ Recurrent local/regional disease of unfavorable biology who achieved a PR after treatment with NBL-CT-I and NBL-CT-II with or without a subsequent operation. (Note) Free of ileus, ANC > 1,000/ $\mu$ L, Hemoglobin > 10 g/dL before RT.
- ◆ All NBL-HR at the end of conventional chemotherapy or >28 days post-HSCT and fulfill the following: (1) APC > 1,000/ $\mu$ l; (2) No requirement for PLT transfusion; (3) Mucositis nearly resolved; (4) ALT < 80 U/L, Bil < 1.5 mg/dl, No VOD (if liver in the field); (5) No respiratory distress on room air (if lung or trachea in the field); (6) Alb > 3 g/dl without albumin infusion for 1 week (if abdominal irradiation); (7) Cre < 1.5 mg/dl (if kidney in the field); (8) No hematuria (if kidney or bladder in the field)

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## RADIOTHERAPY GUIDES -2

### 2. Dosage :

- ◆ For NBL-LR children other than stage 4S, total 2,100 cGy (e.g. 150 cGy x 14 fractions).
- ◆ For NBL-IR children other than stage 4S, total 2,400 cGy (e.g. 150 cGy x 16 fractions).
- ◆ For children with stage 4S disease, 150 cGy x 3 fractions for the liver
- ◆ For NBL-HR: total 3,500 cGy for those with conventional therapy and 2,160 cGy (e.g. 180 cGy x 12 fractions) for those with myeloablative therapy over primary site and metastatic sites.

### 3. Critical Organs :

- ◆ Peritoneal cavity: < 1,500 cGy for contralateral kidney.
- ◆ Thorax: < 1,500 cGy for 2/3 or more of the lung volume.
- ◆ Liver: < 1,500 cGy for 2/3 or more of the liver volume.

### 4. Extent:

2 cm margin in all directions around the residual tumor (pre-operative volume if surgery before RT)

## RESPONSE ASSESSMENT

- (1) To measure treatment response, International Neuroblastoma Response criteria will be used as in [APPENDIX III](#). Measurable tumor is defined as the products of the largest x widest perpendicular diameters. Elevated urine catecholamine levels and quantitative tumor cell invasion of bone marrow are also considered measures of tumor.
- (2) Content and time schedule of evaluation for each treatment assignment is listed in each protocol.

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癌症藥物停藥準則

影像學檢查，若腫瘤反應為NR或PD (定義請見[APPENDIX III](#)「反應標準」)，應停止或改變治療方式。

# 兒癌 – Neuroblastoma

高雄榮民總醫院  
臨床診療指引

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## APPENDIX I. International Neuroblastoma Staging System (INSS) -1

STAGE	Description
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline <sup>1</sup> , with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for Stage 4S).
Stage 4S	Localized primary tumor (as defined for Stage 1, 2A or 2B) with dissemination limited to skin, liver, and/or bone marrow <sup>2</sup> (limited to infants <1 year of age).
Stage X <sub>M</sub>	Multiple primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript “M” (e.g. 3 <sub>M</sub> ).

## APPENDIX I. International Neuroblastoma Staging System (INSS) -2

1. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column. A midline tumor that was Stage 3 (bilateral due to direct extension) prior to operation but was gross totally resected AND had histologically negative lymph nodes OR had lymph nodes sought but not found will be Stage 1 disease. Gross totally resected bilateral tumors in which lymph nodes were not sought or with histologically POSITIVE lymph nodes will be Stage 3 disease.
2. Marrow involvement in Stage 4S should be minimal, i.e., less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or marrow aspirate. More extensive marrow involvement would be considered to be Stage 4. The MIBG scan (if performed) should be negative in the marrow.



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## APPENDIX II. Assignment of Risk Group Protocol -1

**Table 1. Assignment of Risk Group Protocol After Biology Study**

INSS Stage	Age	MYCN Status	Shimada Histology	TPOG-NBL Assignment
1	0 – 21 y	Any	Any	LR
2A, 2B	< 365 d	Any	Any	LR
	≥ 365 d – 21 y	Non-Amp	Any	LR
	≥ 365 d – 21 y	Amp	Fav	LR
	≥ 365 d – 21 y	Amp	Unfav	HR
3	< 365 d	Non-Amp	Any	IR
	< 365 d	Amp	Any	HR
	≥ 365 d – 21 y	Non-Amp	Fav	IR
	≥ 365 d – 21 y	Non-Amp	Unfav	HR
	≥ 365 d – 21 y	Amp	Any	HR
4	< 365 d	Non-Amp	Any	IR
	< 365 d	Amp	Any	HR
	≥ 365 d – 21 y	Any	Any	HR
4S	< 365 d	Non-Amp	Fav	LR
	< 365 d	Non-Amp	Unfav	IR
	< 365 d	Amp	Any	HR

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## APPENDIX II. Assignment of Risk Group Protocol -2

**Table 2. Assignment of Symptomatic Patients Before Biology Study**

Age	2A, 2B	3	4	4S
< 365 d	Low	Intermediate	Intermediate	Low
> 365 d – 21 y	Low	Intermediate	High	-

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## APPENDIX III. International Neuroblastoma Response Criteria

Response	Criteria
<b>Complete Response (CR)</b>	Total disappearance of tumor, with no evidence of disease; urine catecholamines are normal..
<b>Very Good Partial Response (VGPR)</b>	Primary tumor has decreased by 90-99%, no evidence of metastatic disease; urine catecholamines are normal; residual bone scan changes are allowed.
<b>Partial Response (PR)</b>	$\geq 50\%$ decrease in the size of all measurable lesions; the number of positive bone sites is decreased by $> 50\%$ ; no more than one positive bone marrow site allowed; if this represents a decrease in the number of positive sites at diagnosis.
<b>Mixed Response (MR)</b>	No new lesions, $> 50\%$ reduction of any measurable lesion (primary or metastasis) with $< 50\%$ reduction in other lesions and $< 25\%$ increase in any lesion.
<b>No Response (NR)</b>	No new lesions, $< 50\%$ reduction and $< 25\%$ increase in any lesion.
<b>Progressive Disease (PD)</b>	Any new lesion; increase in any measurable lesion by $> 25\%$ ; previous negative bone marrow positive for tumor.

## Reference

1. TPOG\_N2002\_neuroblastoma., [http://www.ccfroc.org.tw/content\\_sub\\_page.php?level1ID=12&level2ID=2](http://www.ccfroc.org.tw/content_sub_page.php?level1ID=12&level2ID=2)