高 雄 榮 民 總 醫 院
神經母細胞瘤診療原則

2024年03月25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 N2020 potocol V1(2021/1/18)

會議討論

上次會議：2023/03/28

本共識與上一版的差異

上一版	新版
1.放上Assignment of Risk Group Protocol表格(ppt.5)。 2.放上maintanence therapy表格(ppt.20、21)。	1.TPOG N2020版本無新增或修改protocol， 故2024年僅審視未修。 2. Dinutuximab納入健保給付，相關規定見ppt 22。

兒癌–Neuroblastoma

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◎危險群分類

1. Very Low Risk : Stage L1, any age, without MYCN amplification,
   Stage MS, without MYCN amplification and 11q deletion, without LTS
2. Low Risk : Stage L2, any age , without MYCN amplification and 11q deletion
   Stage M, age < 18m, without MYCN amplification, but with hyperdiploid
   Stage MS, without MYCN amplification and 11q deletion, with LTS
3. Intermediate Risk: Stage L2, any age, without MYCN amplification, but with 11q deletion
   except age > 5y with undifferentiated/poor differentiated type
   Stage M, age < 18m, without MYCN amplification, but with diploid
4. High Risk : Any Stage, any age, with MYCN amplification
   Stage M, age ≧ 18m
   Stage L2, age > 5y with undifferentiated/poor differentiated type
5. Perinatal : Stage L1, age < 3m

§ LTS: life threatening symptoms
§L1/L2: 依INRG stage
- INRG stage (包括image defined risk factor<IDRF>)及LTS見以下ppt說明

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◎Assignment of Risk Group Protocol

INGR Pre-Treatment Classification

INGR Stage	*MYCN*	Age	Histological Category/ Grade of Tumor Differentiation	11q deletion	Ploidy (only for <18m & M stage)	Pre-treatment Risk Group
L1	NA	any	any	any		Very Low
	Amp	any	any	any		High
L2	NA	< 18m	any	No		Low
				Yes		Intermediate
		≧18m	Any except age > 5y, undifferentiated/ poor differentiated	No		Low
				Yes		Intermediate
		>5y	undifferentiated/ poor differentiated	any		High
	Amp	any	any	any		High
M	NA	<18m	any	any	Hyperdiploid	Low
					Diploid	Intermediate
		≧18m	any	any		High
	Amp	any	any	any		High
MS	NA	<18m	any	No		Very Low/ Low
	Amp	<18m	any	any		High

NA: non amplification

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International Neuroblastoma Risk Group Staging System (INRG)

Stage	Description
L1	Locoregional tumor without IDRFs
L2	Locoregional tumor with one or more IDRFs
M	Distant metastatic disease (except Ms)
MS	INRG Stage L1 or L2 tumor with metastatic disease confined to skin and/or liver and/or bone marrow

Life Threatening Symptoms (LTS)

Intraspinal neuroblastoma
Systemic upset
Pain requiring opiate treatment
Gastrointestinal : Vomiting needing NG/IV support ; BW loss >10%
Respiratory : without evidence of infection but tachypnoea >60 ; oxygen need or ventilatory support
Cardiovascular System: HTN; IVC compression
Renal : impaired renal function; poor urine output(<2mL/kg/hour); hydroureter/hydronephrosis
Hepatic: abnormal liver function >2 ULN; evidence of DIC; platelets <50 x 10^9/L
Bladder/Bowel dysfunction secondary to a mass effect.
A very large tumor volume causing concern of possible tumor rupture and/or the possible rapid development of systemic upset

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APPENDIX V. Image Defined Risk Factors (IDRF)

Anatomic region	Description
Ipsilateral tumor extension within two body compartments	Neck-chest, chest-abdomen, abdomen-pelvis
Neck	Tumor encasing carotid and/or vertebral artery and/or internal jugular vein Tumor extending to base of skull Tumor compressing the trachea
Cervico-thoracic junction	Tumor encasing brachial plexus roots Tumor encasing subclavian vessels and/or vertebral and/or carotid artery Tumor compressing the trachea
Thorax	Tumor encasing the aorta and/or major branches Tumor compressing the trachea and/or principal bronchi Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal	Tumor encasing the aorta and/or vena cava
Abdomen/pelvis	Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumor encasing branches of the superior mesenteric artery at the mesenteric root Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing the aorta and/or vena cava Tumor encasing the iliac vessels Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that:	More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/ structures	Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but *not* considered IDRFs	Multifocal primary tumors Pleural effusion, with or without malignant cells Ascites, with or without malignant cells

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TREATMENT ASSIGNMENT: TPOG-N2020-VLR

1. If patient is stage L1, arrange total tumor excision then follow up.
2. If patient is stage MS without LTS, please keep close follow-up. Surgical resection of primary tumor is not indicated. If progression disease (PD) or life threatening symptoms (LTS) develops in follow-up, the treatment would upgrade to low risk protocol.
3. pre-survey: history, physical examinations, CBC/Diff/Plts, PT, PTT, LDH, ferritin, ALT, bil, creatinine, urinalysis, urine 12/24 hr VMA, CT/MRI of primary/metastatic sites, MIBG/PET/bone scan, BM aspirations and biopsies for stage MS , tumor biology studies for all patients.
4. Post-surgical evaluations for patients

	Mos 1	Mos 2	Mos 3	Mos 6	Mos 9	Mos 12	Mos 18&24	Yearly
Hx, PE	X	X	X	X	X	X	X	X
CBC/Diff/Plts	X	X	X	X	X	X	X	X
Urine VMA			X[1]	X[1]	X[2]	X[2]	X[1]	X[2]
CT/MRI[3]			X	X		X		
Echo	X	X[5]	X	X	X[5]	X	X	X
BMA/Bx[4]			X	X[2]		X[2]	X[2]	X[2]
MIBG/PET			X[5]	X[2]		X[2]	X[2]	X[2]

1. Do only if abnormal at diagnosis.
2. Do only when abnormal at latest study.
3. Use MRI if it provides more information (e.g. spinal). Use the same image modality throughout the study.
4. Do only for patients with stage MS with marrow positive at diagnosis.
5. Do only for patients with stage MS

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TREATMENT ASSIGNMENT: TPOG-N2020-LR

Stage L2

Treat with VP/Carbo x 4 courses.

- If IDRFs become negative, consider surgery.
- If IDRFs are still positive and histopathology are Ganglioneuroblastoma-Intermixed (Schwannian stroma-rich) type at the time of presentation, consider close follow-up or debulking surgery for relief of symptoms.
- If IDRFs are still positive and histopathogy are **NOT** Ganglioneuroblastoma-Intermixed type at the time of presentation, consider debulking surgery, then CADO x 2 courses.

Stage M

Treat with VP/Carbo x 2 courses.

- if LTS is negative, treat with VP/Carbo x 2 courses.
- if LTS is positive, treat with CADO x 2 courses.

Then re-evaluate the disease status

- if IDRFs become negative and metastatic remission achieve, consider surgery, then follow up
- if IDRFs are still positive and metastatic remission achieve, consider debulking surgery, then CADO x 2 courses.
- if IDRFs are still positive and metastatic remission do not achieve, consider CADO x 4 courses. Then follow up closely.

Stage MS with LTS

Treat with VP/Carbo x 2 courses.

- if LTS becomes negative, follow up closely.
- if LTS is still positive, treat with CADO x 2 courses.
- If LTS does not respond rapidly enough to chemotherapy, consider radiotherapy.

Note : Surgical resection of primary tumor is not indicated in this group

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TREATMENT ASSIGNMENT: TPOG-N2020-IR

Stage L2

Treat with VP/Carbo x 2 courses then CADO x 2 courses.

Then re-evaluate the disease status:

- if IDRFs become negative, consider surgery, then VP/Carbo x 1 course + CADO x 1 course.
- If IDRFs are still positive and histopathology is NOT undifferentiated/poor differentiated type at the time of presentation, consider debulking surgery, then CADO x 2 courses.
- If IDRFs are still positive and histopathology is undifferentiated/poor differentiated type at the time of presentation, consider debulking surgery and CADO x 2 courses. Then radiotherapy and 6 courses of 13 cis-retinoid acid treatment are suggested.

Stage M

Treat with VP/Carbo x 2 courses then CADO x 2 courses.

Then re-evaluate the disease status:

- if IDRFs become negative and metastatic remission achieve, consider surgery, then VP/Carbo x 1 course + CADO x 1 course.
- if IDRFs are still positive and metastatic remission achieve, consider debulking surgery, then CADO x 2 courses.
- if IDRFs are still positive and metastatic remission do not achieve, consider CADO x 4 courses.

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TREATMENT ASSIGNMENT: TPOG-N2020-IR

Pre-study evaluations included history, physical examinations,CBC/Diff/Plts, PT, PTT, LDH, ferritin, ALT, bilirubin, creatinine, urinalysis, urine 12/24 hr VMA, CT/MRI of primary/metastatic sites, MIBG/PET/bone scan, BM aspirations and biopsies, tumor biology studies for all patients; and audiogram/ABER, echocardiogram for patients planned for chemotherapy.

Post-chemotherapy evaluations for TPOG-NBL2020-LR/IR

Month	PE	CBC/Diff/Plt	CT/MRI	Echo		Creat#	VMA**	Audio ABER
1	X	X		X		X		
3	X	X	X	X		X	X	
6	X	X	X	X			X	
9	X	X		X				
12	X	X	X	X			X	X
15	X	X						
18	X	X	X*	X			X	
21	X	X						
24	X	X	X*	X			X	X
30	X	X						
36	X	X	X*	X			X	
Yearly	X	X	X*	X*			X	

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NOTE UNDER CHEMOTHERAPY

Baktar prophylaxis 150 mg/m2 TMP component/day in 2 divided doses 3 times/wk on consecutive days

Chemotherapy doses are adjusted for children less than 365 days of age or who are ≦ 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：VP/carbo (etoposide, carboplatin)

Courses of VP/Carbo are given at 21 day intervals

DAY	1	2	3
Carboplatin	X	X	X
Etoposide	X	X	X

DRUG	Dose (mg/kg)	Dose (mg/m^2)
Carboplatin	6.6 mg/kg	200 mg/m^2 in 5% dextrose (5 ml/kg) over 1 hr daily x 3
Etoposide (VP16)	5.0 mg/kg	150 mg/m^2 in 0.9% saline (12.5 ml/kg) over 2 hrs daily x 3

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化學治療處方建議表:CADO (cyclophosphamide, doxorubicin, vincristine)

Courses of CADO are given at 21 day intervals

DAY	1	2	3	4	5	6	7	8
Cyclophosphamide	X	X	X	X	X			
Doxorubicin				X	X			
Vincristine	X							X

DRUG	Dose (mg/kg)	Dose (mg/m^2)
Cyclophosphamide	10 mg/kg	300 mg/m^2 in 5% dextrose (5 ml/kg) over 1 hr, daily x 5 days
Doxorubicin	1 mg/kg	30 mg/m^2 in 0.9% saline over 6 hours on days 4 and 5
Vincristine	0.05 mg/kg	1.5 mg/m^2 (max 2mg) Bolus injection on days 1 and 8

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TREATMENT ASSIGNMENT: : N2020-HR flowchart

Eligibility for PBSCT Consolidation

1 Patients with CR, VGPR, or PR are encouraged to proceed to PBSCT; patients with NR or MR may proceed to PBSCT or receive other experimental regimens; patients with PD may receive other experimental regimens.

2 Sufficient stem cells: ≥ 3 x 10^6 CD34 cells/kg

3 ALT, bili < 3x normal

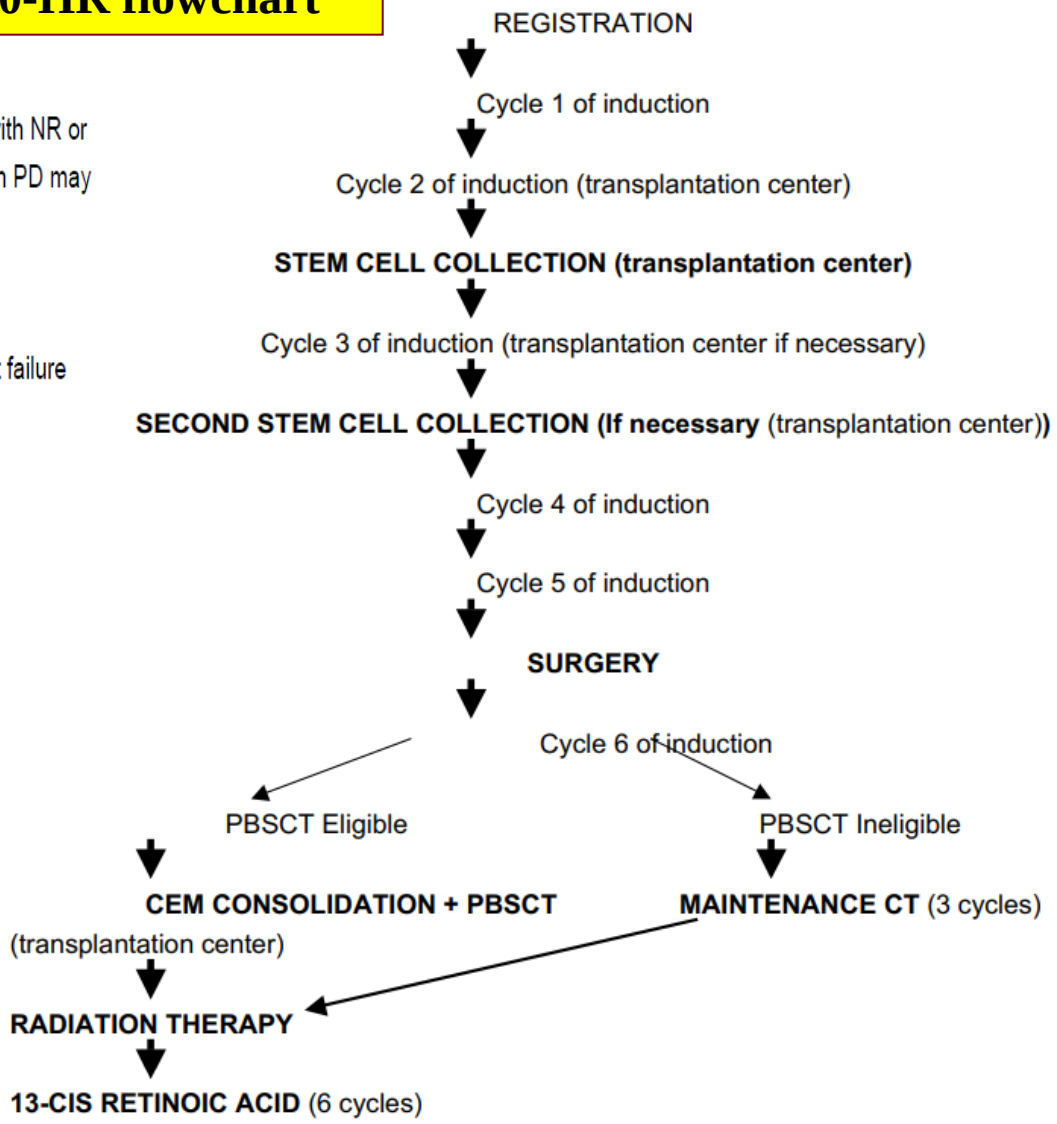
4 Shortening fraction ≥ 28%, or ejection fraction ≥ 55%, no clinical congestive heart failure

5 CCR ≥ 60 ml/min/1.73 m^2

6 Patients with uncontrolled (culture or biopsy positive) infections are not eligible.

7 Patients who are pregnant or lactating are not eligible.

8 HIV seropositive patients are not eligible.



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化學治療處方建議表:N2020-HR (con.)

Chemotherapy

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

Day 0&1

Cyclophosphamide 2100mg/m^2 (70mg/kg)* for 6 hours

Oncovin# 0.67mg/m^2 for 24 hours

Adrimycin 25mg/m^2 (0.83mg/kg)* for 24 hours

Day 2

Oncovin# 0.67mg/m^2 for 24 hours

Adrimycin 25mg/m^2 (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^2 (6.67mg/kg)* for 2 hours

Cisplatin 50mg/m^2(1.66mg/kg)* for 1 hour

Day 3

Cisplatin 50mg/m^2(1.66mg/kg)* for 1 hour

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

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化學治療處方建議表:N2020-HR (con.)

Chemotherapy for PBSCT

	BUMEL MAT									
DRUG	DOSE	DAY	-7	-6	-5	-4	-3	-2	-1	0
Busulfan	< 9 kg: 16.0mg/kg 9 kg to < 16 kg: 19.2 mg/kg 16 kg to 23 kg: 17.6 mg/kg >23 kg to 34 kg: 15.2 mg/kg >34 kg: 12.8 mg/kg			↓	↓	↓	↓			↓ Stem cell infusion
MELPHALAN	140 mg/m^2 I.V. short infusion (15') **not before 24h after last** busulfan dose								□↓	

13-cis-Retinoic Acid therapy

Begin at day +100 after PBSCT; no RT for over 5 days

13-cis-RA 160mg/m^2/day (5.33mg/kg/day)* for BID, for 14 days, followed by 14 days rest per cycle, for 6 cycles

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化學治療處方建議表:N2020-HR (con.)

Table 4. Required Observations During Follow-up After Completion of 13-cis-Retinoic Acid[1]

Observ.	3 M	6 M	9 M	1 Y	1.5 Y	2 Y	2.5 Y	3 Y	3.5 Y	4 Y	4.5 Y	5 Y	Y	At Rel
PE[1], Ht[1], Wt[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC[1], DC[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	
EKG, ECHO[2]				X								X		
BMA &Bx	X			X										X
Tumor Imaging		X	X	X	X	X	X	X						X
MIBG/PET	X	X		X	X	X	X	X						X
24 hr urine VMA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform Status				X		X		X		X		X		
TSH,T4, PFT[3]				X										

1. Perform PE and CBC, PLT, DC monthly for one year after transplant.
2. If abnormal, repeated annually. If child is < 5 yrs, an additional test should be done at 5 yrs.
3. Perform PFT (pulmonary function test) if child is ≥ 5 yrs. If child is < 5 yrs, delay until he is 5 yrs.

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化學治療處方建議表:N2020-HR (con.)

Chemotherapy with *abnormal renal function(Ccr<100ml/min/1.73m2)*
Carboplatin using modified Calvert formula or 10mg/kg if ≦ 12kg total dose (mg/day) = (CCR x BSA/1.73 + 15 x BSA) x 4.1 **Etoposide** 200mg/m^2(6.7mg/kg)*4 for 24 hours **Melphalan** 60mg/m^2(2mg/kg)* 3

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

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化學治療處方建議表:N2020-HR (con.)

Maintenance therapy

13-cis-Retinoic Acid Therapy

- Begin at day +100 after PBSCT.
- LFT < Gr2 toxicity, normal RFT, no proteinuria, no > Gr1 hematuria, Ca/UA/TG ≤ 2N
- No RT for over 5 days
- Dosage: 13-cis-RA 160 mg/m^2/day (5.33 mg/kg/day if ≤ 12 kg) for b.i.d. for 14 days, followed by 14 day rest per cycle with total of 6 cycles.
- Supportive care: topical vitamin E, avoid sun exposure
- Criteria prior to each cycle: a. ALT < 5N, b. skin toxicity < Gr1, c. serum TG < 300 mg/dL, d. No hematuria/proteinuria, e. serum creat < 1.5 mg/dL

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化學治療處方建議表:N2020-HR (con.)

Maintenance therapy (optional)

Dinutuximab and 13-cis-Retinoic Acid (13-cis RA) Therapy will start after completion of radiotherapy

Treatment Schema

Cycle 1-5

Day 1-5/10	Dinutuximab 100 mg/m2 in 5 or 10 days continuous infusion in 0.9% NaCl total 100 mL
Day 1-10	GM-CSF 250 mcg/m2 SC qd for minimum 10 days or longer until ANC > 1500/μL
Day 15-28	13-cis-RA 160 mg/m2/day (5.33 mg/kg/day if < 12 kg) b.i.d. for 14 days, followed by 14 days rest per cycle with total of 6 cycles.

Cycle 6

Day 15-28	13-cis-RA 160 mg/m2/day (5.33 mg/kg/day if < 12 kg) b.i.d. for 14 days

	Course 1	Course 2	Course 3	Course 4	Course 5	Course 6
D 1-5/10	Dinutuximab	Dinutuximab	Dinutuximab	Dinutuximab	Dinutuximab	
D 1-10	GM-CSF	GM-CSF	GM-CSF	GM-CSF	GM-CSF	
D 15-28	13 Cis-RA	13 Cis-RA	13 Cis-RA	13 Cis-RA	13 Cis-RA	13 Cis-RA

Dinutuximab beta (如 Qarziba)：(112/8/1健保給付修正規定)

1.限用於年齡12個月以上的初診斷高危險神經母細胞瘤病人之初次使用GD2免疫治療；且在接受自體幹細胞移植前至少達到部分緩解，在自體幹細胞移植後，可申請 以1次治療所需的5個療程為限。
2.限移植後12個月內開始使用。
3.自初診斷至使用本品前，出現復發、新轉移或疾病惡化者，不得申請給付。
4.經事前審查核准後使用。

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SURGERY GUIDES

1. 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).

2. Tumors suitable for resection at presentation:
   - L1 by INRG definition (localized tumor: IDRF negative)

   Tumors suitable for biopsy only at presentation:
   - L2 by INRG definition (localized tumor: IDRF positive)
   - M and MS tumors by INRG definition (metastatic disease)*

   *Excision of the primary tumor may be an alternative diagnostic procedure to biopsy in metastatic tumors, provided the primary tumor is IDRF negative.

3. If a tumor remains IDRF positive after chemotherapy this is not an absolute contraindication to surgery. Resection may still be recommended if evaluation of the primary tumor suggests that the risk to life, or of major functional loss, is less than the risk from leaving residual disease.

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RADIOTHERAPY GUIDES -1

7.1 Indications

- Symptomatic low risk patients with stage MS that have not responded rapidly enough to chemotherapy.
- Intermediate risk patients with unfavorable biology (undifferentiated/poor differentiated type) who achieved a PR after treatment.
  (Note) Free of ileus, ANC > 1,000/μL, Hemoglobin > 10 g/dL before RT

- All High risk at >28 days post-HSCT and fulfill the following: (1) ANC > 1,000/μl; (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 low risk children with stage 4S disease, 150 cGy x 3 fractions for the liver
◆ For intermediate risk children with unfavorable biology (undifferentiated/poor differentiated type) who achieved IDRF positive after treatment, 2,160 cGy (e.g. 180 cGy x 12 fractions) over primary site
◆ For high risk children, 2,160 cGy (e.g. 180 cGy x 12 fractions) 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)

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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。

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APPENDIX III. International Neuroblastoma Response Criteria

Response	Primary tumor	Metastatic Sites
CR	No tumor	No tumor; catecholamines normal
VGPR	Decreased by 90-99%	No tumor; Residual ^{99}Tc bone changes allowed
PR	Decreased by > 50%	All measurable sites decreased by > 50% Bones and bone marrow : Number of positive sites decreased by > 50%; no more than 1 positive bone marrow site allowed in biopsy.
MR	No new lesions; > 50% reduction of any measurable lesion (primary or metastases) with < 50% reduction in any other; < 25% increase in any existing lesion.	
NR	No new lesions; < 50% reduction but < 25% increase in any existing lesion.	
PD	Any new lesion; increase of any measurable lesion by > 25% ; previous negative marrow positive for tumour.	

CR : Complete Response ; VGPR : Very Good Partial Response ; PR : Partial Response;
MR : Mixed Response ; NR : No Response ; PD : Progressive Disease