高 雄 榮 民 總 醫 院
神經母細胞腫瘤診療原則

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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_neuroblastoma

會議討論

上次會議：NA

本共識與上一版的差異

上一版	新版
1.無。	1.2018年將癌症收案對象兒童(<18歲)區分出來，故新制定兒童癌症-神經母細胞腫瘤診療指引。

兒癌－Neuroblastoma

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◎Aims

(1)To improve the outcome of neuroblastoma patients in Taiwan utilizing modern treatment schemes developed by Western countries

(2)To prepare for participation in international trials that utilize novo biologic strategies such as differentiation, apoptosis, immunomodulation, etc.

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◎評估

-病史、理學檢查
-營養及日常體能狀態
-胸部X光
-血液常規
-電解質及肝腎功能
-腫瘤指標(VMA urine)
-腹部超音波
-腹部電腦斷層攝影(CT)*
-胸部電腦斷層攝影(CT)*
-核磁共振檢查(MRI)
-正子攝影檢查(PET)
-心臟超音波
-骨髓穿刺(Bone marrow punture)
-全身骨骼掃描(Bone scan) *

*與癌症期別相關之主要檢查

◎ RISK ASSIGNMENT AND MONITOR

(1) Diagnostic age, INSS stage (APPENDIX I), the number of copies of the proto-oncogene MYCN present in the tumor cell genome, and Shimada histopathology will be utilized to define risk groups and to determine therapy in this study (APPENDIX II).

(2) To facilitate the future collaboration in international trial, the neuroblastoma biology will be centrally reviewed including pathology, MYCN determination, and oligonucleotide array expression profiling in Neuroblastoma Reference Laboratory (Tzu Chi) and Dr. Seeger's laboratory (CHLA). Furthermore, detection of minimal residual disease in peripheral blood, bone marrows as well as stem cell preparations will also be provided.

※ For symptomatic patients necessitating immediate therapy before characterization of neuroblastoma biology (APPENDIX II), the treatment strategy could be assigned according to diagnostic age and stage. However, second-cycle chemotherapy should be in accord with the final biology characterization.

◎ 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

◎ 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/mm3 and the platelet count >75,000/mm3 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. Indications

- 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/μL, 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/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)

◎ RADIOTHERAPY GUIDES

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.

◎ 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 m2 respectively.

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 <1.5 x normal; Bilirubin <1.5 x normal and AST/ALT <2.5 x normal; Shortening fraction of >27% by echocardiography.

◎ CHEMOTHERAPY PROTOCOL

※NBL-CT-I

Cycle 1 (Carboplatin/Etoposide)

Day 0

Hour 0: Carboplatin 560 mg/m2 (18 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 1: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 3: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Days 1 & 2

Hour 0: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

◎ CHEMOTHERAPY PROTOCOL

※NBL-CT-I

Cycle 2 (Carboplatin/Cyclophosphamide/Doxorubicin)

Day 0

Hour 0: Carboplatin 560 mg/m2 (18 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 1: Cyclophosphamide 1000 mg/m2 (33 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 2: Doxorubicin 30 mg/m2 (1 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 3: 2.5% G/S at 125 ml/m2/hr IVD for 3 hours

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

◎ CHEMOTHERAPY PROTOCOL

※NBL-CT-I

Cycle 3 (Cyclophosphamide/Etoposide)

Day 0

Hour 0: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Hour 2: Cyclophosphamide 1000 mg/m2 (33 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 3: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S (maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 5: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Days 1 & 2

Hour 0: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S (maximum concentration 0.4mg/ml) IVD for 2 hours

◎ CHEMOTHERAPY PROTOCOL

※NBL-CT-I

Cycle 4 (Carboplatin/Etoposide/Doxorubicin)

Day 0

Hour 0: Carboplatin 560 mg/m2 (18 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 1: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 3: Doxorubicin 30 mg/m2 (1 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 4: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Days 1 & 2

Hour 0: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

◎ CHEMOTHERAPY PROTOCOL

※NBL-CT-II

Cycle 5 (Cyclophosphamide/Etoposide)

Day 0

Hour 0: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Hour 2: Cyclophosphamide 1000 mg/m2 (33 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 3: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S (maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 5: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Days 1 & 2

Hour 0: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S (maximum concentration 0.4mg/ml) IVD for 2 hours

◎ CHEMOTHERAPY PROTOCOL

※ NBL-CT-II

Cycle 6 (Carboplatin/Cyclophosphamide/Doxorubicin)

Day 0

Hour 0: Carboplatin 560 mg/m2 (18 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 1: Cyclophosphamide 1000 mg/m2 (33 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 2: Doxorubicin 30 mg/m2 (1 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 3: 2.5% G/S at 125 ml/m2/hr IVD for 3 hours

◎ CHEMOTHERAPY PROTOCOL

※ NBL-CT-II

Cycle 7 (Carboplatin/Etoposide)

Day 0

Hour 0: Carboplatin 560 mg/m2 (18 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 1: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

Hour 3: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Days 1 & 2

Hour 0: Etoposide 120 mg/m2 (4 mg/kg) in 300 ml/m2 2.5% G/S
(maximum concentration 0.4mg/ml) IVD for 2 hours

◎ CHEMOTHERAPY PROTOCOL

※ NBL-CT-II

Cycle 8 (Cyclophosphamide/Doxorubicin)

Hour 0: 2.5% G/S at 125 ml/m2/hr IVD for 2 hours

Hour 2: Cyclophosphamide 1000 mg/m2 (33 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 3: Doxorubicin 30 mg/m2 (1 mg/kg) in 125 ml/m2 2.5% G/S IVD for 1 hour

Hour 4: 2.5% G/S at 125 ml/m2/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/μl and platelet > 100,000/μl for those not in CR.

◎ CLINICAL ASSESSMENT

1. Pre-study evaluations included history, physical examinations, body surface area, CBC/Diff/Plts, PT, PTT, LDH, ferritin, ALT, bil, creat, urinalysis, urine 24 hr VMA, CT/MRI of primary, bone scan, MIBG, bilateral BM aspirations and biopsies, tumor biology studies for all patients; and audiogram/ABER, echocardiogram for patients planned for chemotherapy.

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◎ CLINICAL ASSESSMENT

2. Post-surgical evaluations for patients without chemotherapy

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

① Do only if abnormal at diagnosis.
② Do only when abnormal at 12 months or later. Repeat until negative for 1 year.
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 4S with marrow positive at diagnosis.

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◎ CLINICAL ASSESSMENT

3. Evaluations for patients with chemotherapy for TPOG-NBL2002-LR/IR

	Prior to Chemotherapy	Prior to Each Cycle	LR After Cycle 4*	IR After Cycle 4	IR After Cycle 8*
Hx, PE, BSA	X	X	X		X
CBC/Diff/Plts	X	X	X		X
LDH, ferritin[1], ALT, bil, creat	X	X[1]	X[1]		X[1]
Urinalysis	X	X	X		X
Urine VMA[2]	X		X[2]	X[2]	X[2]
CT/MRI of TU[3]	X		X	X	X
Bone scan	X		X		X
MIBG scan[4]	X[4]		X[4]		X[4]
BMA/Bx[5]	X		X[5]	X[5]	X[5]
Audiogram ABER[6]	X		X		X
Echocardiogram	X		X		X

① Obtain ferritin at Pre-study and prior to chemotherapy; repeated only if elevated.
② Do only if abnormal at diagnosis.
③ Use MRI if it provides more information (e.g. spinal). Use the same image modality throughout the study.
④ MIBG and bone scan are both done at diagnosis, subsequently choose the most sensitive indicator.
⑤ Do for all patients with chemotherapy.
⑥ Obtain ABER if patient can not cooperate for audiogram.

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◎ CLINICAL ASSESSMENT

4. Post-chemotherapy evaluations for TPOG-NBL2002-LR/IR

Month	PE	CBC/Diff/Plt	CT/MRI	Echo	Creat#	VMA"	Audio ABER
2	X	X			X		
4	X	X	X		X	X	
6	X						
8	X	X	X			X	
10	X						
12	X	X	X	X		X	X
15	X						
18	X	X	X*			X	
21	X						
24	X	X	X*	X		X	X
30	X						
36	X	X	X*			X	
Yearly	X	X	X*			X	

* Do only if disease found at month 12, and repeat until negative for two consecutive studies.

Repeat until normal x2.

" Do only if abnormal at diagnosis.

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◎ APPENDIX I. International Neuroblastoma Staging System (INSS)

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[1], 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[2] (limited to infants <1 year of age).
Stage X_M	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_M).

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

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

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
Complete Response (CR)	Total disappearance of tumor, with no evidence of disease; urine catecholamines are normal..
Very Good Partial Response (VGPR)	Primary tumor has decreased by 90-99%, no evidence of metastatic disease; urine catecholamines are normal; residual bone scan changes are allowed.
Partial Response (PR)	≥ 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.
Mixed Response (MR)	No new lesions, > 50% reduction of any measurable lesion (primary or metastasis) with < 50% reduction in other lesions and < 25% increase in any lesion.
No Response (NR)	No new lesions, < 50% reduction and < 25% increase in any lesion.
Progressive Disease (PD)	Any new lesion; increase in any measurable lesion by > 25%; previous negative bone marrow positive for tumor.

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◎ APPENDIX IV. OUTLINE OF TPOG-N2002-HR1

Day 1-7 Cy, Day 8 DDP, Day 10 Ep
↓
Day 22-28 Cy, Day 29-31 VP
↓
Day 43-49 Cy, Day 50 DDP, Day 52 Ep
↓
Day 72 DDP, Day 73-75 VP
↓
Day 92-98 Cy, Day 99 DDP, Day 101 Ep
↓
Day 120-126 Cy, Day 127-129 VP
↓
Surgery
↓
After wound healing
Day 1-7 Cy, Day 8 Ep
↓
Day 21 DDP, Day 22-24 VP
↓
Day 41-47 Cy, Day 48 Ep
↓
Day 60 DDP, Day 61-63 VP
↓
R/T 3500 cGy
↓
13-RA

Cy　Cyclophosphamide 150 mg/m^2 IV or PO QD X 7 days

DDP　Pre-Hydrate with normal saline 10 ml/kg over 1 hour.
Anti-emetics (e.g. Zofran 0.15 mg/kg 30 min before chemotherapy, then q8h)
Mannitol 8 g/m^2/ IV over 15 minutes
Cisplatin 90 mg/m^2/day in 400 ml/m^2 half saline over 2 hours

Hydration with D5W0.45% NaCl + 30 mEq/L KCl + 500 mg/L
MgSO4 + 250 mg/L Ca gluconate at 200 ml/m^2/hr for 6 hours
plus 20% Mannitol at 35 ml/m^2/hr (7 gm/m^2/hr) IV for 6 hours

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

Ep　Epirubicin 35 mg/m^2 IVP

VP　Etoposide 225 mg/m^2/day in 500 ml/m^2 normal saline over 2 hrs X 3 days
Hydration with D5W0.45% NaCl + 30 mEq/L KCl at 125 ml/m^2/hr

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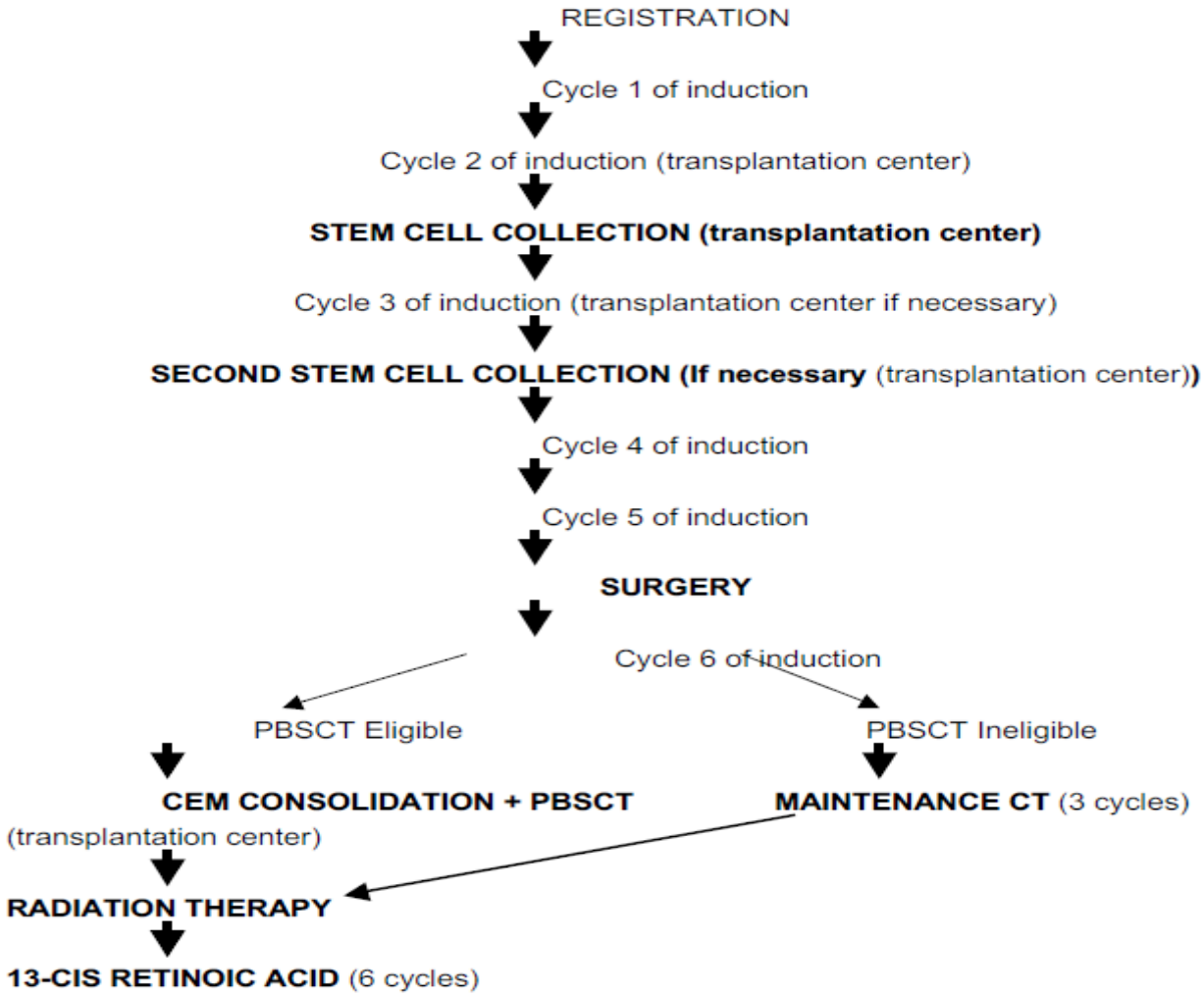
◎ APPENDIX V. OUTLINE OF TPOG-N2002-HR2 and -HRrel



◎癌症藥物停藥準則

影像學檢查，腫瘤有復發或變大情況，應停止或改變治療方式。

Reference

1. TPOG_N2002_neuroblastoma., http://www.ccfroc.org.tw/content_sub_page.php?level1ID=12&level2ID=2