중추신경계 베아종(germinoma)에서 전보조합암화요법 및 방사선 병합치료의 유용성에 관한 다기관 임상연구

I. 연구개요(Schema)

1. 연구 배경(Background)

중추신경계 베아종(germinoma)은 방사선에 매우 예민하여 방사선치료만으로 72~90%의 높은 완치율을 보이는 종으로서 16 오랫간 동안 방사선치료가 주된 치료방법으로 사용되어 왔다. 두개내 벤세포종양(germ cell tumor) 환자에서 대부분이 청소년이면서 완치율이 높다는 점을 고려한다면 완치율을 높이려는 노력뿐 아니라 치료 이후의 삶의 질을 향상시키려는 노력도 매우 중요하다고 하겠다. 삼

이 질을 향상시키는 노력으로서 방사선치료에 수 반되며 후유증을 최소화하기 위하여 현재의 높은 완치율을 유지하는 방향 내에서 조사된 방사선량을 전자적으로 검토시켜 연구가 여러 기관에서 진행되었다. 저점 치료 용기에 대한 논란도 계속되었다.

따라한데에는 원발 병소에 조사된 방사선량이 50 Gy를 상회하는 경우7,10도 있었으며, 중추신경계 베아종은 조직학적 형태가 고환의 seminoma나 난소의 dysgerminoma에서의 조직학적 형태와 동일하되 초기 seminoma에서 사용되는 25~30 Gy 정도의 방사선량으로도 중추신경계 순수 베아종의 완치될 수 있음을 제시하였고11 실제로 Aydin 등11이 중추신경계 순수 베아종으로 방사선치료 도중 사망하였던 1예를 보급한 결과 조사된 방사선량이 16 Gy에 불과하였음에도 병리학적으로 완전판례

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1 unit Gy, ( ) cumulative doses to primary sites, RT: Radiotherapy, CT: Chemotherapy, CSI: Craniospinal irradiation, CR: Complete Remission, PR: Partial Remission, Fraction size: 1.5 Gy for CSI, 1.8 Gy for Local RT.

Korean Society for Pediatric Neuro-Oncology Protocol for Germ Cell Tumors

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대한소아암학회지
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들 알 수 있었고 보고한 것을 사라지 않도록 많은 연구가들 정격적으로 방사선량을 줄여가는 시도를 해 왔다. Fields 등은 조직학적으로 두개골 내 배어중으로 화양된 환자에서 원반방사 46 Gy 이하를 조사하였던 7례 중 제받은 1례도 없었다고 보고하였고, Chang 등은 원반방사조사에서 제받된 방사선량이 45 Gy 이하였던 15례 중 제받한 경우는 1례도 없었음을 보고하면서 원반방사조사 이용방법 방사선량을 45 Gy 이하로 감소시키며 제방이 위험성은 없을 것이라고 주장하였다.

방사선치료용과 관련하여서는 뇌척수조사(cerebrospinal iradation, CSI)를 통한 치수촉의 예방적 방사선조사 여부가 논란이 대재 과다이다. 두개골 내 배어중의 치수촉 전반 선도는 10~30%로 보고되고 있다.14, 15) 그러나 방사선치료 후 원반방사조사에 방사선치료 방해 없이 두개골 분실이 나타나는 경우는 극히 드물고(0.4%) CSI를 시행함으로써 통계적으로 유의적인 치료결과가 항상 가지지 못하였다 보고하고 있다. 또한 CSI를 통한 치수촉의 예방적 방사선조사를 시행함으로써 이득이 있는 환자는 조직학적으로 배어중이 확인된 경우의 15%에 불과하다고 보고하고 있으며(15) CSI의 수반집 수있는 성장장애나 생식기능의 위험성을 고려하여서 체포하되므로 치수촉이 이후 배어중의 전이가 확인된 경우 혹은 다른 방법으로 치수촉이 증가한 경우에만 가동하여 CSI를 할 것을 주장하고 있는 보고가 있다.16, 17) 또한 방사진치료로 치수촉의 해부학적 해석이 비록 낮지만 제방 이후에는 효과적인 치료방법이 없고,20, 21) CSI를 시행함으로써 치수촉에서의 해부학적 해석이 0%로는 임상적 모두 두개골 내 배어중 환자에게 CSI를 시행할 것을 제시하고 있다. Chang 등은 CSI를 시행한 7례 중 제방한 경우는 1례도 없어서 0%의 제방율을 보고하지만, 치수촉이 제방될 경우는 효과적인 치료방법이 없고 정상적인 치수촉에 조사되는 방사선량을 20 Gy 수준으로 낮추므로 CSI에 수반될 수 있는 후유증에 대한 변단이 감소하였다는 점을 고려한다면 CSI를 시행하는 것이 높은 환자율을 유지하면서도 제방이 위험성은 제거할 수 있는 방법이라고 주장하였다.

시장록 등은 1971년부터 2000년까지 방사선 단독치료를 시행받은 69명의 환자를 대상으로 후방적 연구조사를 한 결과 focal field RT, whole brain, RT, 그리고 CSI를 시행한 환자 중 각각 11례, 8례, 50례었다. 이 중 나머지 4명의 환자에서 제방이 중앙이나 이 쌍했는지, 3례는 focal field 방사선치료로 받은 환자에서 다른 1례는 whole brain 방사선치료를 받은 환자에서 생겼으며, CSI를 시행 받은 50례의 환자에서는 제방이 없었다. CSI를 시행 받은 환자의 치수촉 조사방 방사선량 분포를 보면 48% (24/50)의 데에서 20~25 Gy의 방사선을 조사받았으며, 34% (17/50)의 데에서 20 Gy 보다 이하 방사선치료를 받았으며, 18% (9/50)의 데에서 25 Gy보다 높은 방사선을 시행하였다.

상기의 경험들은 바탕으로 대한방사선학회 소아방사선 전문가들이 두개골 내 배어중에 대한 치수촉 방사선치료 및 방사선치료의 지침에 대한 방사선치료의 방사선치료를 받은 18% (9/50)의 데에서 25 Gy보다 높은 방사선치료를 시행하는 것을 표준치료법으로 권장하였다.

최근에는 두개골 내 배제방사선이 항암학요법에도 많은 반응을 보이는 경계 관찰하여 방사선치료로이 시제받을 가능한 후후증을 감소시키기 위해 항암학요법을 병행하면서 방사선치료용을 조합하되 조사되는 방사선량을 줄이는 노력이 시도되고 있다. Allen 등이 전산조차학요법을 시행한 후 조사되는 방사선량을 원반방사조사 30 Gy, 치수촉치료는 20~21 Gy까지 감소시키고도 각각 11 예 중 1례에서 제방이 나타났다고 보고하였다. 그 후 Buckner 등이 두개골 내 배제방사선 17계 (배제방사선 9계)에서 51개월의 중앙추적관찰기간 동안 치수촉에 제방이 나타난 배제 1계를 제외한 나머지 16례에서는 모두 제방이 없었고 제방이 있었던 1례의 경우 치수촉 방사선치료를 통한 치료결과 성공적이 하였다. 둘째 17계 모두가 무방병증 중이고 치료에 따른 후후증은 생존율에 미치지 않았다고 보고하면서 전산조차학요법이 유용성이 강조되고 있다.

하지만, 항암학요법과 방사선치료의 병용요법
2. Objectives

2.1 To compare event free survival (EFS) after radiotherapy alone (regimen A) to chemotherapy followed by response based radiotherapy (regimen B)

2.2 To assess complete response rate after regimen A or B

2.3 To estimate toxicity of chemotherapy (regimen B)

2.4 To compare treatment morbidity (Verbal learning and memory, executive function, quality of life)

3. Patient eligibility criteria

3.1 Patient with newly diagnosed histologically confirmed primary CNS pure germinoma should be enrolled and start therapy within 28 days of diagnostic biopsy.

3.2 Age: ≥3 and ≤25

3.3 Marker profiles

Serum and CSF β-HCG ≤ 50 mU/mL
Serum AFP ≤ 10 ng/mL
CSF AFP ≤ 2.0 ng/mL

3.4 Adequate bone marrow reservoir (hemoglobin ≥ 10.0 g/dL, absolute neutrophil count ≥ 1,000/µL, platelet ≥ 100,000/µm³), renal function (serum creatinine ≤ 1.0 mg/dL) and hepatic function (total bilirubin < 1.5 mg/dL, SGOT/SGPT < 200 U/L)

3.5 Diagnostic MRI must have been performed

3.6 Patient must have signed an informed consent form.

4. Patient Evaluation

4.1 Complete history and physical examination

4.2 Preoperative cranial MRI (repeat within 72 hours post-op)

4.3 Pre- or post-op spine MRI

4.4 CBC with differential and blood chemistries

4.5 Preoperative serum marker

4.6 CSF markers, before biopsy and intraoperative

4.7 CSF cytology (lumbar) post-op 1 or 2 week

4.8 Endocrine studies, height, weight

4.9 Detailed neurological examination

4.10 Assessment of quality of life

5. Registration Procedure

5.1 Patient can be registered only after pretreatment evaluation is completed and eligibility criteria are met.

5.2 Patients will be registered prior to any protocol therapy by calling (KSPNO 질환번호).

- The patient will be registered to a treatment arm and a case number will be assigned.

5.3 Initially all the patients will be subdivided into two subgroups according to disease extent: solitary vs disseminated

5.3.1 Definition of dissemination: Brain/spine MRI (pre- or post-op) or intra-operative evidence of nodular intraventricular or leptomeningeal metastases

- Cytologically positive post-op lumbar CSF.
- Tumor in pineal and suprasellar region.
- Tumor in pineal gland with diabetes insipidus (with/without suprassellar tumor).

6. Neurosurgical guidelines

6.1 Type of surgery

The goal of the operation should be to get tissue specimen for histologic diagnosis. Any surgical type such as resective craniotomy, endoscopic biopsy, or stereotactic biopsy can be used.

6.2 Definition of extent of resection
Biopsy only: If tumor removal is less than 10% of the total tumor mass.

Partial resection: The surgical removal of greater than 10%, but less than 50%, of the tumor mass.

Subtotal resection: The surgical removal of greater than 50%, but less than 90%, of the tumor mass.

Gross total resection: Resection of greater than 90% of the tumor mass.

6.3 Required data submission

The neurosurgical tumor resection form and a copy of the institutional operative report will be completed and submitted by the neurosurgeon.

7. Radiation Therapy

7.1 Target Volume

7.1.1 Craniospinal irradiation
- Whole brain and spinal canal should be irradiated.

7.1.2 Local irradiation (Local RT)

7.1.2.1 Local RT target volume in case of solitary tumor with CR response to CT would be involved field or whole ventricle according to physician’s preferences.

7.1.2.2 Prescribed dose should irradiate PTV (Planning Target Volume).

7.1.2.3 PTV in involved field or whole ventricular field represents primary tumor/or whole ventricle plus margin

7.1.2.4 Target volume definition in involved field

RT

Gross tumor volume (GTV): gross disease as defined by the preoperative MRI

Clinical target volume (CTV): GTV plus areas considered to contain microscopic disease. CTV will be defined as GTV plus 1 cm margin in this study.

Planning target volume (PTV): PTV will provide a margin around the CTV to compensate for variability in treatment setup or patient motion. PTV will be defined as CTV plus 0.5 cm margin in this study.

7.2 Radiation dose

7.2.1 Solitary lesion

7.2.1.1 RT alone

→ Craniospinal irradiation: 19.5 Gy/1.5 Gy fx &

→ Local RT: 19.8 Gy/1.8 Gy fx

7.2.1.2 Combined chemoradiotherapy

a. if CR after chemotherapy

→ No CSI

→ Local RT: 30.6 Gy/1.8 Gy fx.

b. if PR after chemotherapy:

→ Craniospinal irradiation: 19.5 Gy/1.5 Gy fx &

→ Local RT: 19.8 Gy/1.8 Gy fx

7.2.2 Multiple or disseminated lesion

7.2.2.1 RT alone

→ Craniospinal irradiation: 24 Gy/1.5 Gy fx &

→ Local RT: 16.2 Gy/1.8 Gy fx

7.2.2.2 Combined chemoradiotherapy

a. if CR after chemotherapy

→ Craniospinal irradiation: 19.5 Gy/1.5 Gy fx &

→ Local RT: 10.8 Gy/1.8 Gy fx

b. if PR after chemotherapy:

→ Craniospinal irradiation: 24 Gy/1.5 Gy fx.

→ PTV: 16.2 Gy/1.8 Gy fx

7.3.1 Treatment technique

7.3.1.1 Beam energy

Megavoltage equipment is required with effective photon energy.

7.3.1.2 Treatment planning

7.3.1.2.1 Craniospinal Irradiation

- The patient is positioned prone with the forehead resting on a rigid head support.

- The spine field is simulated with the cephalad margin on the neck but without exiting through the mouth.

- The cranial fields are set up so that their caudal field margins are parallel with the diverging cephalad margin of the spinal field
- In case that spinal axis cannot be covered fully within a field, the field should be separated. The fields may be separated on the skin surface so that the junction point lies upon the posterior of the spinal cord.
- At least once junction movement should be done to avoid cold & hot point during the CSI treatment
- CT-simulation based planning is not mandatory.
- See Appendix 5

7.3.1.2 Local RT
- 3-Dimensional conformal radiotherapy is recommended for Local RT, but is not mandatory.
- In case of 2-Dimensional conventional treatment planning, at least three beam ports should be used for the target.

8. Chemotherapy

8.1 Background and Rationale for the Use of Neoadjuvant Chemotherapy

Although patients with CNS pure germinoma have traditionally been treated with radiation only resulting in excellent survival, many potential late effects of RT prompted the trial of reducing radiation dose or field to lower the incidence and severity of debilitating late effects. Allen et al. reported that only 1 patient relapsed among 11 patients who had received neoadjuvant chemotherapy followed by RT with 30 Gy for the primary site and 20–21 Gy for neuraxis. Buckner et al. emphasized the feasibility of neoadjuvant chemotherapy reporting that all 17 patients were alive disease free without any endocrine and neurocognitive dysfunction following combined chemotherapy and RT, including one patient who were rescued with spinal axis radiation after relapse on the neuraxis. However, there is no report clearly demonstrating the long-term sequelae of the combination therapy. Furthermore, it is uncertain whether the combination of chemotherapy and reduction of RT would have more survival benefits over the toxicities of chemotherapy itself, and could really lower the incidence and severity of late effects compared with RT alone. Therefore, a multi-center prospective study comparing the two arms is to be performed to clarify the optimal treatment protocol.

8.2 Chemotherapeutic Agents

8.2.1 Carboplatin

8.2.1.1 Source and Pharmacology: Carboplatin is a platinum-salt alkylating agent. Carboplatin is not bound to plasma protein; however, platinum is approximately 30% bound. Carboplatin is 60% to 80% excreted through the kidneys. The drug has a volume of distribution of 16 L and an elimination half-life of 3 hours.

8.2.1.2 Formulation and Stability: Available in 50 mg, 150 mg, and 450 mg vials containing lyophilized powder. Store intact vials at controlled room temperature (15–30°C). Reconstitute each vial with D5W to achieve a final concentration of 10 mg/mL or lower (further dilution to concentrations as low as 0.5 mg/mL is acceptable). Carboplatin should be protected from light.

8.2.1.3 Toxicity: Toxicities include myelosuppression, nausea and vomiting, transient liver function abnormalities, paresthesia and high frequency hearing loss. Abnormalities in serum creatinine and creatinine clearance, proteinuria, hypocalcemia, and hypomagnesemia may occur.

8.2.1.4 Guidelines for Administration: IV, diluted in D5W (volume=150 mL/m²) over 4 hours.

8.2.2 Etoposide

8.2.2.1 Source and Pharmacology: A semisynthetic derivative of podophyllotoxin which functions as a mitotic inhibitor, but does not bind microtubules. Its main effect appears to be in the S and G2 phase of the cell cycle. The mean terminal half-life is 11.5 hours with a range of 3 to 15 hours. It is primarily excreted in the urine.

8.2.2.2 Formulation and Stability: A yellow solution
with a pH of 3 to 4, available in 100 mg (5 mL) or 150 mg (7.5 mL) sterile vials. The intact vials are stable for 3 years at room temperature. Vials diluted with NS as recommended (concentration of 0.2 ~ 0.4 mg/mL) are stable for 48 hours at that concentration. Discard if precipitate is noted. Do not refrigerate.

8.2.2.3 Toxicity: Myelotoxicity is most often dose limiting, the granulocyte nadir occurring 7 to 14 days after drug administration. No cumulative toxicity observed. Severe anaphylactic reactions have been observed. Alopecia can occur.

8.2.2.4 Guidelines for Administration: IV, administration over 2 hours. Should not be given by rapid intravenous push. Severe hypotension may occur if the drug is given in less than 30 minutes; hypotension can be managed by slowing infusion rate or increasing the volume of saline administered with the drug. Watch for anaphylaxis.

8.2.3 Cyclophosphamide (CPM)

8.2.3.1 Source and Pharmacology: An alkylating agent, related to nitrogen mustard, which is biochemically inert until it is metabolized to its active components by the liver phosphamidases. It is non-phase-specific. The drug and its metabolites are excreted exclusively by the kidney after parenteral administration. The plasma half-life ranges from 4 to 6.5 hours.

8.2.3.2 Formulation and Stability: Injectable form is available as white crystals with sodium chloride added, in vials containing 200 mg and 500 mg. All preparations are stable at room temperature. Reconstitute with 10 mL sterile water for 200 mg vials and 25 mL for 500 mg vials, respectively. Discard solution after 24 hours at room temperature; stable up to 6 days if refrigerated (2 ~ 8°C). Since there is no preservative, precautions should be taken to insure sterility, or solution be discarded within 8 hours.

8.2.3.3 Toxicity: Acute dose-related toxicity includes myelosuppression, primarily leukopenia, with a nadir of 8 ~ 14 days. MESNA may be used to prevent hemorrhagic cystitis. Therapy must be discontinued if acute hemorrhagic cystitis occurs. Therapy may be restarted if hematuria clears and there is no evidence of a contracted bladder. Other adverse reactions include anorexia, nausea and vomiting, alopecia, SIADH, immunosuppression, and gonadal suppression with associated sterility. Pulmonary fibrosis is rare. Chronic dose-related toxicity includes gonadal dysfunction. The prepubertal gonad is less susceptible. Hormonal function is generally preserved, especially in the male; fertility is mainly affected (spermatogenesis in the male, follicle formation in the female). Sterility may be partially reversible. Gonadal effects during puberty are uncertain; the risk may be increased. Secondary malignancies may occur.

8.2.3.4 Guidelines for Administration: Prehydrate with DSW 1/2 NS plus 20 mEq/L KCl at >300 mL/m²/hr 2 hours prior to administration of CPM. Give CPM IV over 1 hour. Continue hydration with DSW 1/2 NS plus 20 mEq/L KCL at 100 mL/m²/hr for 24 hours.

8.2.4 MESNA (sodium 2-mercaptoethane sulfonate)

8.2.4.1 Source and Pharmacology: MESNA is a thiol compound with the capacity of inhibiting the uro-toxicity of the oxazaphororines, ifosfamide and CPM. Within 1 hour of administration, MESNA is completely oxidized to DiMESNA, a totally inert compound. After an 800 mg dose the half-life for MESNA and DiMESNA is 0.36 hours and 1.17 hours, respectively. There is little or no tissue penetration. Following glomerular filtration, DiMESNA is rapidly reduced in the renal tubules back to MESNA, which inactivates acrolein and the oxazaphosphorinnes, thus preventing bladder toxicity.

8.2.4.2 Formulation and Stability: Available in 200 mg and 400 mg ampules with a concentration of 100 mg/mL. Store intact ampules at controlled room temperature (15 ~ 30°C). MESNA is not light-sensitive, and intact ampules are stable for a period of 5 years from the time of manufacture. For IV administration,
diluted to 20 mg/mL with 5% dextrose or NS. Use within 6 to 8 hours since there is no preservative.

8.2.4.3 Toxicity: A bad taste in the mouth is frequent. At high doses (2.4 g/m²) abdominal pain, nausea and vomiting, headache, limb and joint pain, lethargy, diarrhea, rash, and transient hypotension have been encountered.

8.2.4.4 Guidelines for Administration: IV push

8.3 Exclusion for Chemotherapy

Among all patients that meet the eligibility criteria shown at 3.1 to 3.6, those who are assigned to the RT alone arm are excluded for chemotherapy.

8.4 Chemotherapy Schedule and Drug Dose

Neoadjuvant therapy will consist of four courses of chemotherapy, alternating between course A and B, beginning with course A and ending with course B (A → B → A → B). Courses are to be administered every 21 days, if possible. The fourth course will consist of course B followed by a 4–5 week rest until APC (APC is defined as the absolute number of band and segmented neutrophils, and monocytes) >1,000/mm³ and platelet count >100,000/mm³ at which time radiation therapy will begin.

8.4.1 Course A

Day: 0 1 2 21

Drug: Carboplatin Etoposide Etoposide Course B Etoposide

Day 0

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

Hour 2–6 Carboplatin 450 mg/m² in D5W (volume=150 mL/m²) IV over 4 hours

Day 1, 2

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

8.4.2 Course B

Day: 0 1 2 21

Drug: CPM CPM VP-16 Course A VP-16 VP-16

Day 0, 1

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

Hour 2–3 CPM 1,000 mg/m² in NS (volume=100 mL/m²) IV over 1 hour

MESNA 350 mg/m² as an IV bolus starting with the initiation of CPM

Hour 5 MESNA 350 mg/m² as an IV bolus

Hour 8 MESNA 350 mg/m² as an IV bolus (0, 3, 6 hours after CPM).

Day 2

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

8.4.3 G-CSF/GM-CSF

The preference of either G-CSF or GM-CSF is according to the physician’s choice.

8.4.3.1 G-CSF

5 micrograms/kg/day (150 micrograms/m²/day) SQ daily may be started on the day when ANC is <500/mm³. Continue daily until the post-nadir ANC reaches ≥1,000/mm³. G-CSF must be stopped at least 48 hours before starting the next cycle of chemotherapy.

8.4.3.2 GM-CSF

250 micrograms/m²/day SQ daily may be started on the day when ANC is <1,000/mm³. If BSA <1 m², 250 micrograms/m²/day SQ daily and if BSA ≥1 m², 400 micrograms/day SQ daily. Continue daily until the post-nadir ANC reaches ≥1,500/mm³. GM-CSF must be stopped at least 48 hours before starting the next cycle of chemotherapy.

8.5 Modifications based on Toxicity

8.5.1 Hematologic Toxicity

Toxicities expected from these drugs may include severe leukopenia, anemia, and thrombocytopenia. Each cycle of treatment will commence when the APC is >1,000/mm³ and platelet count >100,000/mm³ without benefit of transfusion and at least 3 weeks from the initiation of the previous course. If counts have recovered, give full dose. No modifi-
cation of subsequent induction chemotherapy doses will be made for fever with neutropenia. Every effort should be made to give full doses and to adhere to this schedule. In order to do this, careful attention to prevention and treatment of infectious complications is essential. In this spirit, delays are preferable to dosage modifications. If hematologic recovery is not sufficient to allow the next cycle to be given at week 4 or 5 and APC is \( > 750/\text{mm}^3 \) and platelet count \( > 750,000/\text{mm}^3 \) without benefit of transfusion, doses should be reduced in 20% decrements. Call the Study Chair if hematologic recovery is still not sufficient more than 2 weeks after the scheduled day (5 weeks from the start of each course).

8.5.2 Hepatotoxicity

For bilirubin (2 × upper normal lab and/or SGOT (AST) (5 × upper normal lab and/or SGPT (ALT)) (5 × upper normal, delay next cycle 1 week, resume if values fall below levels mentioned above. If not, delay on more week. Rule out infectious etiology. If no recovery, call Study Chair. If recovery occurs continue treatment at 80% dose. Escalate to full dose as tolerated.

8.5.3 Renal Toxicity

Prior to each cycle of course A, a creatinine clearance (Ccr) or GFR must be performed. If Ccr falls below 60 mL/min/1.73 m² or (50% of baseline not responsive to hydration, wait for 1 week. If Ccr is still below 60 mL/min/1.73 m² but above 30 mL/min/1.73 m², the carboplatin dose should be reduced by 50% of the calculated dose. If Ccr is below 30 mL/min/1.73 m², then stop chemotherapy and patient will proceed to RT.

8.5.4 Bladder toxicity

Severe hemorrhagic cystitis (gross hematuria with or without clots) may necessitate delay of cyclophosphamide. If the final course (second course R) is delayed because of persistent hemorrhagic cystitis, do not wait for more than 3 weeks and the patient will proceed to RT omitting the final chemotherapy cycle.

8.5.5. Ototoxicity

A decrease in auditory acuity at frequencies above the normal hearing range (4,000 ~ 8,000 Hz) is expected, and does not constitute a contraindication to further therapy. For Grade 0, 1, and 2 ototoxicity, no dosage modification should be made. For Grade 3 ototoxicity, a 50% reduction should be made in carboplatin dosage. For Grade 4 ototoxicity, carboplatin should be held and not resumed unless follow-up audiograms show an improvement in hearing function.

8.5.6 Allergic Reactions

Allergic reactions may occur with etoposide and rarely with carboplatin. Patients who come off drug therapy because of toxicity still remain on study and continue to be followed until death. Before discontinuing the putative offending drugs, attempt premedication with chlorpheniramine 4 mg/m² and hydrocortisone 5 mg/kg along with a more prolonged infusion time with careful monitoring of the patient. If reaction is limited to mild skin reaction, the drug may be continued. Otherwise, the drug must be dropped from the treatment and patient will proceed to RT.

9. Patient assessment

9.1 Study parameters

9.2 Response evaluation

9.2.1 MRI examination

9.2.1.1 RT alone group

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pretreatment</th>
<th>During RT</th>
<th>Prior to each CTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and P/E</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>N/E</td>
<td>X</td>
<td>Weekly</td>
<td>X</td>
</tr>
<tr>
<td>MRI brain/spine</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum HCG/ AFP</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF HCG/ AFP</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>Weekly</td>
<td>X</td>
</tr>
<tr>
<td>blood chemistry</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Endocrine evaluation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-P and QoL</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiogram</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluate at 1 month after treatment with MRI

9.2.1.2 Combined chemoradiotherapy group
MRI should be taken 3 weeks after 2 & 4 cycles of chemotherapy and 1 month after completion of radiotherapy.

9.2.2 Definition of response
Complete response: All lesions are not visible on MRI and positive cytology becomes negative ($\beta$-HCG (if >10) declines to <2 uU/ml)

Very good partial response (VGPR): Suprasellar tumor declines to < 4 mm and pineal tumor declines to <10 mm (same CSF and $\beta$-HCG criteria)

Partial response (PR): Tumor volume decrease (50%) of pretreatment volume.

Stable disease (SD): Neither sufficient decrease in tumor volume for PR, nor sufficient increase in tumor volume for PD.

Progressive disease (PD): Tumor volume increase (25%) of pretreatment volume.

9.3 Observations after completion of treatment

<table>
<thead>
<tr>
<th>Observation</th>
<th>Years 1–2</th>
<th>Years 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/E and N/E</td>
<td>q 4 M</td>
<td>q 6 M</td>
</tr>
<tr>
<td>Height / Height</td>
<td>q 4 M</td>
<td>q 6 M</td>
</tr>
<tr>
<td>MRI brain/spine</td>
<td>q 4 M</td>
<td>q 6 M</td>
</tr>
<tr>
<td>Serum HCG/AFP</td>
<td>Q4 M</td>
<td>q 6 M</td>
</tr>
<tr>
<td>CSF HCG/AFP</td>
<td>If serum marker rise</td>
<td>If serum marker rise</td>
</tr>
<tr>
<td>Endocrine evaluation</td>
<td>Abnormal: q 6M/ WNL: q 12</td>
<td>Same</td>
</tr>
<tr>
<td>N-P and QoL</td>
<td>After RT: 2, 24 M</td>
<td>48 M</td>
</tr>
<tr>
<td>Audiogram</td>
<td>q 12 M</td>
<td>q 12 M</td>
</tr>
</tbody>
</table>

9.4 Quality of life

<table>
<thead>
<tr>
<th>검사 종류</th>
<th>시행가능 여부 (규준 준수 연령)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health Questionnaire, Parent Version (6–18 yr)</td>
<td>Child: K-WISC III 측정기로 정상화</td>
</tr>
<tr>
<td>Pediatric Quality of Life Inventory #4 (8–12 &amp; 13–20)</td>
<td>PSQI 산입 (6–16 yr)</td>
</tr>
<tr>
<td>Short Form-Version 2, Qol Questionnaire Self-Report (≥18 yr)</td>
<td></td>
</tr>
</tbody>
</table>

9.5 Neuropsychological Test

<table>
<thead>
<tr>
<th>검사 종류</th>
<th>시행가능 여부 (규준 준수 연령)</th>
<th>대체 가능 및 보충 검사</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Abbreviated Scale of Intelligence (≥6 yr)</td>
<td>Child: K-WISC III</td>
<td></td>
</tr>
<tr>
<td>Rey Complex Figure Test (≥6 yr)</td>
<td>가능 (7–11 yr)</td>
<td>FSIQ 추정 (6–16 yr)</td>
</tr>
<tr>
<td>California Verbal Learning Test (Child 6–16 yr, Adult 15–16 yr, Adult: ≥17 yr)</td>
<td>가능</td>
<td>CVLT ≥ 16 yr</td>
</tr>
<tr>
<td>Delis-Kaplan Executive Functioning System (≥8 yr)</td>
<td>W.G.S.T ≥ 5 yr</td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities Test (≥8 yr)</td>
<td>Child: K-WISC III</td>
<td>subtest ≥ 16 yr, Adult: K-WAIS, subtest ≥ 16 yr</td>
</tr>
<tr>
<td>ADS attention test</td>
<td>5–15세</td>
<td></td>
</tr>
</tbody>
</table>

10. References

3. Wara WM, Fellows CF, Sheline GF, Wilson CF,


29. Allen IC, Durose EJ, Donahue R, Nirenberg A. A phase II trial of preirradiation carboplatin in newly diagnosed germinoma of the central nervous system.
Cancer 1994;74:940-4

증추신경계 비비아존성 생식세포종에서 carboplatin, etoposide, cyclophosphamide bleomycin 조합 전보조항암화학요법과 방사선 병합 치료의 유용성에 관한 다기관 임상연구

I. 연구개요(Schema)

<table>
<thead>
<tr>
<th>Modality</th>
<th>CSI</th>
<th>Local RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized CT + RT ± OP</td>
<td>36</td>
<td>18 - 23.4 ( (54 - 59.4)^a )</td>
</tr>
<tr>
<td>Disseminated CT + RT ± OP</td>
<td>39</td>
<td>14.4 - 19.8 ( (53.4 - 58.8)^a )</td>
</tr>
</tbody>
</table>

Unit: Gy, ( ) Cumulative doses to primary sites; RT: Radiotherapy, CT: Chemotherapy, OP: Operation, CSI: Craniospinal irradion. Fraction size: 1.5 Gy for CSI, 1.8 Gy for Local RT. \(^a\): Total dose for local RT depends on age and tumor localization in the range of 53.4 to 59.4 Gy.

1. 연구 배경(Background)

두개 내 생식세포종은 방사선에 매우 민감한 종양으로서, 손수 베아존인 경우 전통적으로 방사선 단독 요법이 호반적인 치료로 인식되어 왔으며 완 경율이 72 - 90%에 달한다.\(^b\). 그러나, 손수 베아존인 경우로 달리 때도가 높은 성분을 포함하는 비 비아존성 생식세포종이 경우 전기도수 방사선 조 사를 시행하지라도 방사선 단독 요법만으로는 치료 성적이 저조하였다.\(^c\). 이에 현의 비비아존성 생식 세포종 환자에게 화학요법이 효과적이라는 연구들을 근거로 하여 1980년대 중반부터는 두개 내 비비 아존성 생식세포종에서도 화학요법에 대한 정립이 발표되기 시작하였다. 제한된 치료의 이론이므로 인지하는 가장 적절한 화학요법은 명확한 공통된 의견은 현재까지 없는 상태이다.\(^d\),\(^e\). 한편, Chang 등\(^f\)은 VBPE (vinblastine, bleomycin, cisplatin, and etoposide)로 명명한 항암화학요법과 방사선 치료를 병합하여 좋은 치료 성적을 얻었으나 방사선 치료를 제외한 VBPE 단독 요법은 비비아 존성 생식세포종 치료에比喻분자라고 여겼었다.

방사선 치료와 화학요법이 각각 단독 요법으로는 만성스러운 치료 성적을 보여주지 못하였으므로 최근에는 비비아존성 생식세포종에서 방사선 치료와 화학요법을 병합하는 치료가 선호되고 있는 추세이다. Robertson 등\(^g\)는 ‘화학요법 방사선 치료-화학요법’의 소위 ‘선택취지’ 치료를 시도하여 훨씬 원칙물로 보고하였으며, Ogawa 등\(^h\)의 연구에서는 방사선 단독 요법 군과 화학요법 병합 군이 치료 성적을 각각 44%와 84%로 보고하여 병합 요법의 유용성을 강조하고 있다.

그러나, 두개 내 생식세포종은 그 희귀성으로 인하여 수술, 방사선치료, 화학요법 등이 상대적 중요성에 대해 여전히 논란이 여겨지며, 특히 화학 요법을 사용하다가 항암제에 중복하여 두어 기간이 있어 서의 최적의 방법 역시 검증되어 있지 않다. 많은 연구에서 주로 platinum계 항암제를 사용하고 있으나 표준화된 치료 방법은 없으며, 아직도 여러가지로 각기 다소 다하다. 더욱이 화학요법에 비판되는 많은 장제 지 부작용을 감안할 때 전보조항암화학요법은 보편적으로 허용될 수 있는 수준이 부족을 차지에서 치료 성적의 향상에 결정적인 기여를 한다.

You 등\(^i\)의 보고에 의하면 두개 내 생식세포종에서 방사선치료 또는 cisplatin, cyclophosphamide, etoposide, vincristine 등을 이용한 전보조항암화학요법을 시행하여 비비아존성 생식세포종 환자 9례 중 8례가 무사건 생존하였다. 화학요법으로 인한 사망이나 중증의 이하후유증(mobility)은 발생하지 않았으나 전 예에서 1회 이상 반복으로 인한 입원적
로가 필요하였고, cisplatin에 의한 이독성이 44.4% 에서 발생하였다. 종양이 주로 양측 중심부에서 발생하는 재부착과 특성을 가지므로 전단 시 요량증이 동반될 환자의 비율이 높았고 이러한 상황에서 적절한 수술 근위를 유지하는 것이 어려워 이독성의 비도가 높았던 것으로 해석하였으며 cisplatin 사 용에 대해사는 재고해야 할 필요가 있음을 제시하 였다.

Carboplatin은 cisplatin과 같은 platinum계 약물로 시 cisplatin에 비해 신독성 및 이독성이 적은 것으로 알려져 있다[20], 대한소아이학중앙학회에서는 cisplatin 대신 carboplatin을 근간으로 한 화학요법 을 개발하고 그 효과에 대해 체계적인 연구를 시행 하고자 하였다. 대한소아이학중앙학회 산재 무기 내 생식세포방 위험급에서는 carboplatin과 함께 분통 적으로 두개 내막의 생식세포와 해외적인 것으로 인증되었던 cyclophosphamide, etoposide, bleomy cin 등을 혼합한 화학요법을 개발하였으며 새로운 계 개발된 전산조합형화학요법의 유용성 및 반사 성 방법 요법 후의 적도 심적에 대해 연구하고자 하였다.

두개 내 비배양성 생식세포와의 치유성을 감안할 때, 맏기한 공동 연구를 통한 체계적이고 전 항적인 연구를 통해 새로운 유합형 전산조합형화학요 법의 유용성에 대한 명확한 증명이 요구된다.

2. Objectives

2.1 To determine the event free survival and overall survival of patients with CNS non-germinomatous germ cell tumor treated with neoadjuvant chemotherapy including carboplatin, etoposide, cyclophosphamide, and bleomycin followed by craniospinal irradiation.

2.2 To assess response rate after chemotherapy

2.3 To estimate acute toxicity of chemotherapy

2.4 To compare comparative efficacies of carboplatin-based chemotherapy with historical cisplatin-based chemotherapy.

2.5 To determine the long-term auditory, neurocogni-
5. Registration Procedure

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met.

5.2 Patients will be entered on study by telephoning the Korean Society of Pediatric Neuro-Oncology Operations Center at 82-2- between 9:00 a.m. and 5:00 p.m., Monday-Friday.

The information requested on the study entry registration form will be required at the time of this telephone call. The KSPNO registrar will provide KSPNO study identification number at this time.

6. Chemotherapy

6.1 Background and Rationale for the Use of Neoadjuvant Chemotherapy

Although patients with CNS pure germinoma have traditionally been treated with radiation only resulting in excellent survival, many potential late effects of RT prompted the trial of reducing radiation dose or field to lower the incidence and severity of debilitating late effects. Allen et al.20 reported that only 1 patient relapsed among 11 patients who had received neoadjuvant chemotherapy followed by RT reduced to 30 Gy for the primary site and 20–21 Gy for neuraxis. Buckner et al.21 emphasized the feasibility of neoadjuvant chemotherapy reporting that all 17 patients were alive disease free without any endocrine and neurocognitive dysfunction following combined chemotherapy and RT, including one patient who were rescued with spinal axis radiation after relapse on the neuraxis. However, there is no report clearly demonstrating the long-term sequelae of the combination therapy. Furthermore, it is uncertain whether the combination of chemotherapy and reduction of RT would have more survival benefits over the toxicities of chemotherapy itself, and could really lower the incidence and severity of late effects compared with RT alone.

Therefore, a multi-center prospective study comparing the two arms is to be performed to clarify the optimal treatment protocol.

6.2 Chemotherapeutic Agents

6.2.1 Carboplatin

6.2.1.1 Source and Pharmacology: Carboplatin is a platinum-salt alkylating agent. Carboplatin is not bound to plasma protein; however, platinum is approximately 30% bound. Carboplatin is 60% to 80% excreted through the kidneys. The drug has a volume of distribution of 16 L and an elimination half-life of 3 hours.

6.2.1.2 Formulation and Stability: Available in 50 mg, 150 mg, and 450 mg vials containing lyophilized powder. Store intact vials at controlled room temperature (15–30°C). Reconstitute each vial with D5W to achieve a final concentration of 10 mg/mL or lower (further dilution to concentrations as low as 0.5 mg/mL is acceptable). Carboplatin should be protected from light.

6.2.1.3 Toxicity: Toxicities include myelosuppression, nausea and vomiting, transient liver function abnormalities, paresthesia and high frequency hearing loss. Abnormalities in serum creatinine and creatinine clearance, proteinuria, hypocalcemia, and hypomagnesemia may occur.

6.2.1.4 Guidelines for Administration: IV, diluted in D5W (volume=150 mL/m²) over 4 hours.

6.2.2 Etoposide

6.2.2.1 Source and Pharmacology: A semisynthetic derivative of podophyllotoxin which functions as a mitotic inhibitor, but does not bind microtubules. Its main effect appears to be in the S and G2 phase of the cell cycle. The mean terminal half-life is 11.5 hours with a range of 3 to 15 hours. It is primarily excreted in the urine.

6.2.2.2 Formulation and Stability: A yellow solution with a pH of 3 to 4, available in 100 mg (5 mL) or 150 mg (7.5 mL) sterile vials. The intact vials are
stable for 3 years at room temperature. Vials diluted with NS as recommended (concentration of 0.2-0.4 mg/mL) are stable for 48 hours at that concentration. Discard if precipitate is noted. Do not refrigerate.

6.2.2.3 Toxicity: Myelotoxicity is most often dose limiting, the granulocyte nadirs occurring 7 to 14 days after drug administration. No cumulative toxicity observed. Severe anaphylactic reactions have been observed. Alopecia can occur.

6.2.2.4 Guidelines for Administration: IV, administration over 2 hours. Should not be given by rapid intravenous push. Severe hypotension may occur if the drug is given in less than 30 minutes; hypotension can be managed by slowing infusion rate or increasing the volume of saline administered with the drug. Watch for anaphylaxis.

6.2.3 Cyclophosphamide (CPM)

6.2.3.1 Source and Pharmacology: An alkylating agent, related to nitrogen mustard, which is biochemically inert until it is metabolized to its active components by the liver phosphamidases. It is non-phase-specific. The drug and its metabolites are excreted exclusively by the kidney after parenteral administration. The plasma half-life ranges from 4 to 6.5 hours.

6.2.3.2 Formulation and Stability: Injectable form is available as white crystals with sodium chloride added, in vials containing 200 mg and 500 mg. All preparations are stable at room temperature. Reconstitute with 10 mL sterile water for 200 mg vials and 25 mL for 500 mg vials, respectively. Discard solution after 24 hours at room temperature; stable up to 6 days if refrigerated (2–8°C). Since there is no preservative, precautions should be taken to insure sterility, or solution be discarded within 8 hours.

6.2.3.3 Toxicity: Acute dose-related toxicity includes myelosuppression, primarily leukopenia, with a nadir of 8–14 days. MESNA may be used to prevent hemorrhagic cystitis. Therapy must be discontinued if acute hemorrhagic cystitis occurs. Therapy may be restarted if hematuria clears and there is no evidence of a contracted bladder. Other adverse reactions include anorexia, nausea and vomiting, alopecia, SIADH, immunosuppression, and gonadal suppression with associated sterility. Pulmonary fibrosis is rare. Chronic dose-related toxicity includes gonadal dysfunction. The prepuberal gonad is less susceptible. Hormonal function is generally preserved, especially in the male; fertility is mainly affected (spermatogenesis in the male, follicle formation in the female). Sterility may be partially reversible. Gonadal effects during puberty are uncertain; the risk may be increased. Secondary malignancies may occur.

6.2.3.4 Guidelines for Administration: Prehydrate with D5W 1/2 NS plus 20 mEq/L KCL at 200 ml/m²/hr 2 hours prior to administration of CPM. Give CPM IV over 1 hour. Continue hydration with D5W 1/2 NS plus 20 mEq/L KCL at 100 mL/m²/hr for 24 hours.

6.2.4 MESNA (sodium 2-mercaptoethane sulfonate)

6.2.4.1 Source and Pharmacology: MESNA is a thiol compound with the capacity of inhibiting the urotoxicity of the oxazaphosphorines, ifosfamide and CPM. Within 1 hour of administration, MESNA is completely oxidized to DimESNA, a totally inert compound. After an 800 mg dose the half-life for MESNA and DimESNA is 0.36 hours and 1.17 hours, respectively. There is little or no tissue penetration. Following glomerular filtration, DimESNA is rapidly reduced in the renal tubules back to MESNA, which inactivates acrolein and the oxazaphosphamides, thus preventing bladder toxicity.

6.2.4.2 Formulation and Stability: Available in 200 mg and 400 mg ampules with a concentration of 100 mg/mL. Store intact ampules at controlled room temperature (15–30°C). MESNA is not light-sensitive, and intact ampules are stable for a period of 5 years from the time of manufacture. For IV admini-
stratation, diluted to 20 mg/mL with 5% dextrose or NS. Use within 6 to 8 hours since there is no preservative.

6.2.4.3 Toxicity: A bad taste in the mouth is frequent. At high doses (2.4 g/m²) abdominal pain, nausea and vomiting, headache, limb and joint pain, lethargy, diarrhea, rash, and transient hypotension have been encountered.

6.2.4.4 Guidelines for Administration: IV push

6.2.5 Bleomycin

6.2.5.1 Source and Pharmacology: An antibiotic produced by fermentation from Streptomyces verticil-
ues. Lethal effect-binds and causes scission of DNA molecule. It is cell-cycle phase specific, with its major effect in G1 and M. Its peak blood level post IM injections about 30–60 minutes, and is about one third that of similar dose given IV. Drug has rapid plasma half-life of 10–20 minutes followed by a 2.5 hour terminal half-life. Excreted by the liver and kidney. Catabolized by hydrolase in most tissue.

6.2.5.2 Formulation and Stability: Available in 15 U (15 mg) vials as bleomycin sulfate, a white or yellowish lyophilized powder. Dissolve contents in 5 mL of physiologic saline for IV administration. Intact ampules of sterile powder are stable for 2 years at temperatures of 2–8°C.

6.2.5.3 Toxicity: Acute toxicity: lethal anaphylaco-
toid reaction with severe fever and hypotension leading to renal failure or death (very rare). Significant dose reduction is advised for patients with renal failure. Pneumonitis can occur, progressing to pulmonary fibrosis with a cumulative dose of >400 U. Oxygen inhalation therapy accentuates pulmonary toxicity and should be used with care. It is recommended that follow-up pulmonary function tests, including diffusing capacity (DLCO), be done during course of therapy and for 1 year following completion of same. Other toxicities include nausea, vomiting, anorexia, skin rash, hyperpigmentation and skin tenderness. Immunosuppression is not noted.

6.2.5.4 Guidelines for Administration: IV over 10–30 minutes. (Avoid pure oxygen inhalation therapy)

6.3 Chemotherapy Schedule and Drug Dose

Neoadjuvant therapy will consist of four courses of chemotherapy, alternating between course A and B, beginning with course A and ending with course B (A → B → A → B). Courses are to be administered every 21 days, if possible. The fourth course will consist of course B followed by a 4–5 week rest until APR (APR is defined as the absolute number of band and segmented neutrophils, and monocytes) 1,000/ mm³ and platelet count >100,000/mm³ at which time radiation therapy will begin.

6.3.1 Course A

Day: 0 1 2 21

Drug: Carboplatin Etoposide Etoposide Course B

Etoposide Etoposide Bleomycin

Day 0

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

Hour 2–6 Carboplatin 450 mg/m² in D5W (volu-
me=150 mL/m²) IV over 4 hours

Day 1, 2

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

Hour 2–2:30 Bleomycin 15 mg/m² in NS (volu-
me=50 mL) IV over 30 minutes

6.3.2 Course B

Day: 0 1 2 21

Drug: CPM CPM VP-16 Course A

Etoposide Etoposide Bleomycin

Day 0, 1

Hour 0–2 Etoposide 150 mg/m² in NS (volume=450 mL/m²) IV over 2 hours

Hour 2–3 CPM 2,000 mg/m² in NS (volume=100
mL/m²) IV over 1 hour
MESNA 450 mg/m² as an IV bolus starting with the initiation of CPM
Hour 5 MESNA 400 mg/m² as an IV bolus
Hour 8 MESNA 400 mg/m² as an IV bolus
(0, 3, 6, 9, 12 hours after CPM).

Day 2
Hour 0–2 Etoposide 150 mg/m² in NS (volume= 450 mL/m²) IV over 2 hours
Hour 2–2: Bleomycin 15 mg/m² in NS (volume= 50 mL/m²) IV over 30 hours

6.3.3 G-CSF/GM-CSF

The preference of either G-CSF or GM-CSF is according to the physician's choice.

6.3.3.1 G-CSF

5 micrograms/kg/day (150 micrograms/m²/day) SQ daily may be started on the day when ANC is < 500/mm³. Continue daily until the post-nadir ANC reaches ≥1,000/mm³. G-CSF must be stopped at least 48 hours before starting the next cycle of chemotherapy.

6.3.3.2 GM-CSF

250 micrograms/m²/day SQ daily may be started on the day when ANC is < 1,000/mm³. If BSA < 1 m², 250 micrograms/m²/day SQ daily and if BSA ≥ 1 m², 400 micrograms/day SQ daily. Continue daily until the post-nadir ANC reaches ≥1,500/mm³. GM-CSF must be stopped at least 48 hours before starting the next cycle of chemotherapy.

6.4 Modifications based on Toxicity

6.4.1 Hematologic Toxicity

Toxicities expected from these drugs may include severe leukopenia, anemia, and thrombocytopenia. Each cycle of treatment will commence when the APC is > 1,000/mm³ and platelet count > 100,000/mm³ without benefit of transfusion and at least 3 weeks from the initiation of the previous course. If counts have recovered, give full dose. No modification of subsequent induction chemotherapy doses will be made for fever with neutropenia. Every effort should be made to give full doses and to adhere to this schedule. In order to do this, careful attention to prevention and treatment of infectious complications is essential. In this spirit, delays are preferable to dosage modifications. If hematologic recovery is not sufficient to allow the next cycle to be given at week 4 or 5 and APC is > 750/mm³ and platelet count > 750,000/mm³ without benefit of transfusion, doses should be reduced in 20% decrements. Call the Study Chair if hematologic recovery is still not sufficient more than 2 weeks after the scheduled day (5 weeks from the start of each course).

6.4.2 Hepatotoxicity

For bilirubin (2 × upper normal lab and/or SGOT (AST) (5 × upper normal lab and/or SGPT (ALT) (5 × upper normal, delay next cycle 1 week, resume if values fall below levels mentioned above. If not, delay on more week. Rule out infectious etiology. If no recovery, call Study Chair. If recovery occurs continue treatment at 80% dose. Escalate to full dose as tolerated.

6.4.3 Renal Toxicity

Prior to each cycle of course A, a creatinine clearance (Ccr) or GFR must be performed. If Ccr falls below 60 mL/min/1.73 m² or (50% of baseline not responsive to hydration, wait for 1 week. If Ccr is still below 60 mL/min/1.73 m² but above 30 mL/min/1.73 m², the carboplatin and bleomycin doses should be reduced by 50% of the calculated doses. If Ccr is below 30 mL/min/1.73 m², then stop chemotherapy and patient will proceed to RT.

6.4.4 Bladder toxicity

Severe hemorrhagic cystitis (gross hematuria with or without clots) may necessitate delay of cyclophosphamide. If the final course (second course B) is
delayed because of persistent hemorrhagic cystitis, do not wait for more than 3 weeks and the patient will proceed to RT omitting the final chemotherapy cycle.

6.4.5. Ototoxicity

A decrease in auditory acuity at frequencies above the normal hearing range (4,000 – 8,000 Hz) is expected, and does not constitute a contraindication to further therapy. For Grade 0, 1, and 2 ototoxicity, no dosage modification should be made. For Grade 3 ototoxicity, a 50% reduction should be made in carboplatin dosage. For Grade 4 ototoxicity, carboplatin should be held and not resumed unless follow-up audiograms show an improvement in hearing function.

6.4.6 Allergic Reactions

Allergic reactions may occur with etoposide, bleomycin, and rarely with carboplatin. Patients who come off drug therapy because of toxicity still remain on study and continue to be followed until death. Before discontinuing the putative offending drugs, attempt premedication with chlorpheniramine 4 mg/m² and hydrocortisone 5 mg/kg along with a more prolonged infusion time with careful monitoring of the patient. If reaction is limited to mild skin reaction, the drug may be continued. Otherwise, the drug must be dropped from the treatment and patient will proceed to RT.

7. Radiation Therapy

8. Patient assessment

<table>
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<th>Assessment</th>
<th>Pretreatment</th>
<th>During RT</th>
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<td>Audiogram</td>
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</tbody>
</table>

8.1 Study parameters

8.2 Response evaluation

- Evaluate at 1 month after treatment with MRI

8.2.1 Complete response: All lesions are not visible on MRI and positive cytology becomes negative (β-HCG (if >10) declines to <2 uU/ml)

8.2.2 Very good partial response (VGPR): Suprasellar tumor declines to <4 mm and pineal tumor declines to <10 mm (same CSF and (HCG criteria)

8.2.3 Partial response (PR): Tumor volume decrease ≥50% of pretreatment volume.

8.2.4 Stable disease (SD): Neither sufficient decrease in tumor volume for PR, nor sufficient increase in tumor volume for PD.

8.2.5 Progressive disease (PD): Tumor volume increase ≥25% of pretreatment volume.

8.3 Observations after completion of treatment

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<td>q 12 M</td>
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8.4 Quality of life

Spitzer quality of life index (SQLI)
Child Health Questionnaire, Parent Version (6~18 yr)
PedsQL Quality of Life Inventory #4 (8~12 & 13~20)
Short Form-Version 2, QoL
8.5 Neuropsychological Test

Wechsler Abbreviated Scale of Intelligence (≥ 6 yr)
Rey Complex Figure Test (≥ 6 yr)
California Verbal Learning Test (Child 6~16 yr, Adult ≥ 17 yr)
Delis-Kaplan Executive Functioning System (≥ 8 yr)
Symbol Digit Modalities Test (≥ 8 yr)

9. References

Korean Society for Pediatric Neuro-Oncology Protocol for Germ Cell Tumors

Audiol 1999;28:139-43