ADJUVANT CHEMOTHERAPY AND RADIATION IN MEDULLOBLASTOMA AFTER SURGERY

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INTRODUCTION

Medulloblastoma is a malignant embryonic tumor consisting largely of primitive or poorly differentiated cells which are felt to originate in the neuroepithelial roof of the fourth ventricle. (1,9,19,22) Medulloblastoma are not truly encapsulated, but a clear interface can often develop between the tumor and surrounding brain and the aim of surgery is total resection of the gross visible tumor, except when located within the brainstem (9). Only 38% of primary brain tumors were diagnosed with in the first month after the onset of symptoms. Incomplete neurologic maturation and non union of the suture allow for some compensation, and brain tumors in younger children may remain silent for prolonged periods. (1,9)

Between 25% and 30% of brain tumors are medulloblastoma (13,6). With the use of computed tomography, brain tumors can be recognized with greater certainty and treated earlier. (2,19) Typical initial non specific complaints are headache (diffuse, frontal, occipital), vomiting (projectile, or non projectile) lethargy, irritability, and other behavioral changes. (12,14)

The survival rate for patients with medulloblastoma has slowly risen over the past four decades. Improvement in out come has been due to multiple factors including refinements in surgical techniques, the routine use of craniospinal radiation and adjuvant chemotherapy. (16)

Several variables are now believed to have an impact on the out come of these patients including : the size of the tumor at the time of diagnosis, the extent of the tumor resection, The stage, age, radiation dose, and more effective chemo-therapy. (6,8,16,20)

The standard treatment of medulloblastoma has been surgery followed by post operative craniospinal irradiation, (3) although it is conceivable that less differentiated tumors were more radio sensitive (7). But the age at which the child receives cranial irradiation must be considered. Studies of children with brain tumors have suggested that the younger the age of the child at the time of treatment, the more serious the intellectual deficit will be. (4,5,20) For this reason in children less than 2 years of age, we endeavored to reduce the dosages of radiation. (3,6,15,16)
Recently, chemotherapy has been added to these modalities of therapy in an attempt to improve the out-look. (3,8,9, 10,13,16)
Effects of treatment must be considered and a long term fol low-up should be done.

The purpose of this case report paper is to present the first experience with adjuvant chemotherapy cople with sur-gery and irradiation therapy in medulloblastoma in a child of 16 months.

CASE REPORT

Y,a 16 month-old Indonesian boy was admitted to the Department of Child Health Dr. Soetomo Hospital on June 11, 1993 with the main complaint of vomiting.

The history as told by the mother was as follows :

The patient suffered from non projectile vomiting since 4 days before admission, 3 or 4 times a day.

One month previously he suffered from low grede fever, cough, coryza and vomiting. The mother took him to a general practitioner.

The vomiting continued but the fever and cough disappeared.

The doctor recommended hospitalization for further evaluation.

On May 5, 1993 the boy was admitted to the Lumajang Hospital, staying there for 6 days and discharged from the Hospital vomiting. But vomiting recurred several days later, before admission to Dr. Soetomo Hospital.

The immunizations were up to date. The growth and development was within normal limit and the occurrence of other diseases in the past was denied except for respiratory tract infection 2 - 3 times a year. He was the only child in the family.

Physical examination on admission revealed a slightly malnourished boy with a body weight of 9,3Kg. There was no anemia, jaundice, cyanosis or dyspnea, but the eyes were sunken. The body temperature was $37^{o}C$. The pulse rate was 114 perminute and the respiratory rate was 24 perminute. The

blood pressure was 110/70mmHg. Skin turgor was poor.
The heart and lungs were normal. The liver and spleen were not palpable. The extremities were normal.
Laboratory examination revealed : Hb 12,5gg/dl, WBC 6.200, PVC 36%. The platelet were sufficiant in number.
The stool and urine examination were normal, serum electrolyte, sodium 123meq/l, potassium 3,45meq/l. Arterial blood gas analysis : pH 7,48, PCO_2 30,8, pO_2 119,9, HCO_3 23, BE : (+) 1,3.

The working diagnosis on admission was vomiting for further investigation with the DD of peptic ulcer, obstruction of the intestinal tract, SOP with moderate dehydration, and brain tumor.
The patient was treated with normal Saline for rehydration, urine culture and upper GI series were planned.

An upper GI study on the following days showed no abnormalities, and urine culture was negative. Urine culture was negative. The patient was week and the vomiting persisted.
Six days later the condition became worse; apathy and periodic apnea were noted. Physical examination revealed a right hemiparesis and slow pupil reaction, the head circumference is 49cm.
Increased intracranial pressure was suspected. A skull CT-scan was performed to confirme the diagnosis.

Skull CT-scan showed dilatation of the ventricle system and there was a hyperdense area at the posterior fossa measuring 9 x 5cm, suggesting Hydrocephalus and a posterior fossa tumor. We consulted the neuro surgeon, who decided to do an urgent VP shunt for decompression of the intracranial pressure.

With the VP shunt, the condition improved. The patient and contact was good. The eyes deviated to the right side and nystagmus was noted.

Craniotomy could be performed 3 weeks after the VP shunt, when the pneumonia resolved.

The surgeon found a large tumor measuring 7x6x3cm, filling the fourth ventricle.

The tumor crumbled and bled easily. The surgeon excised the tumor in toto.

Pathologic examination showed : Macroscopically, the tumor weigh 75gram, an crumbly Microscopically, the Pathologist found the tumor was vascular and cellular with hyperchromation of the nucleus, some of it were arranged in pseudorosettes.

The post operative condition was 6000.

Two weeks after the operation the eyes appeared normal but the lower extremities were still paralyse. Fisio therapy dept treated the patient for this disturbance.

Craniospinal irradiation and adjuvant chemotherapy were started 20 days after the operation.

We needed consultations with the Radiologic department to decide on the radiation dose. Because the patient gave chemotherapy so the radiation dose should be reduced. Standard protocol in Radiologic department is 11.000 rads if without chemotherapy and 4500 rads for patient with adjuvant chemotherapy.

Craniospinal irradiation was planned to delivered over a total 6 weeks in fractions of 100-200rads per day, 5 days a week Vincrsitine and Metotrexate with Dexamethasone gave a weekly during radiation therapy.

Peripheral blood examination was performed a weekly to evaluated hemmatologic effect of chemo and radiation therapy.

As long as the treatment, there were 3 times the chemo and radiotherapy was postponed because reducing Hb and Leukopenia.

To evaluated the evidence recurence of the tumor cerebrospinal fluid examination and skull Ct-scan were performed.

Three months after the operation CT-scan evaluation showed no evidence tumor and dilated ventricular system still existed.

The cerebrospinal fluid examinatin on the 4 months after the operation revealed : clear cerebrospinal fluid, no tumor cells, Monocyte 388, PMN was negative, Glucose 40mg protein 30mg.

The patient was discharged after completed the irradiation treatment and continued the chemotherapy policlinicaly.

DISCUSSION :

The diagnose of medullablastoma is usually established with pathologic examination. The tumor histological pattern is vascular and is characterized by deeply staining nuclei with scant cytoplasm arranged in pseudorossettes. In our case, microscopicaly of the tumor was similar with these pattern. (11,17)

Direct effects of tumor and/or increased intracranial pressure may play a part in clinical manifestation such as vomiting, lethargic, motor deficits and complaining of severe headache. (1,4,9,14)

Increased intracranial pressure may arise from the mass effect of the tumor it self and from ventricular obstruction. (9,12)

Additional manifestation of increased intra cranial pressure include diplopia or strabismus, or both (associated with damage to cranial nerve VI or III). (12)

In our case, the major symptom was recurrent vomiting with decreased of consionsness. Paralyse of the interior extremities and the eyes at out word posisition. The laboratory examination were done still in normal limit, e.g : The upper GI examination periphheral blood examination, serum electrolyte, liver function test and renal function test.

The further examination skull Ct-scan examination revealed midline posterior fossa mass with mass measuring 9x5cm, there was ventriculer system delatation, conclude posterior fossa

tumor with hydrocephalus. So, vomiting in our case cause by increasing intracranial pressure or by the tumor.

Cohen and duffns, 1984 noted that vomiting is secondary effect of increasing intracranial pressure or cause by direct irritating to nerve X or vomiting central in bottom of fourth ventricle.

In young patients, the delay may be due to the in ability of the child to discribe complaint's such as headaches or diplopia. And in infants with non union of the sutures, a space occupying mass with increasing intracranial pressure may be accommodated for sometime before an increase in head size or focal symptoms are noted. (1) In our case the diagnose established after 1 month from first time symptom of vomiting.

Flores (1986) reported the mean interval from the appearance of symptoms to diagnosis in patient with brain tumors was 10,8 weeks.

Ct-scan has simplified diagnosis and has likely resulted in earlier diagnosis in many cases (16). Typical Ct-scan findings of a medulloblastoma are a midline posterior fossa area. (19)

In our case the diagnosis of medulloblastoma was suggestible with Ct-scan and established with pathological examination.

The goal of surgery is total resection of gross visible tumor, except for that located within the brainstem. (9)

Complete resection was accomplished in our patient.

Before operation the patient was performed shunting procedures, for decompression of increasing intracranial pressure. Options for acute management include preoperative administration of corticosteroid, tumor excision and preoperative shunting. (9)

The 5 year survival rates were 59%, 49% and 30% for patients perform radical excision, sub total exicision and partial excision. (14)

In our case, the tumor excised intoto making better prognosis.

Medulloblastoma is a highly malignant tumor and has the ability to metastasise widely through the subarachnoid space. (11) With earlier treatment the dessimination can prevent.

The standard treatment of a medulloblastoma has been surgery followed by postoperative cranispinal irradiation; the survival rate at five years is approximately 40% to 60%. (3,14)

Since medulloblastoma is an embryonic tumor, cytotoxic agent might be expected to be of value in the treatment of this disease, in view of the success of chemotherapy in other primitive tumour of childhood. (13)

The survival of children receveiving adjuvant chemotherapy was twice that for children treated without chemotherapy. (13,16)

Sutton (1991) reported that the major change in survival was seen in the poor-risk group, who received adjuvant chemotherapy.

In our case after surgery and cranio spinal radio therapy the patient gave adjuvant chemo therapy with vincristine, metotrexate and dexametahasone. Unfortunately, whole-brain radiation can cause permanent and progressive neuro psychological damage, especially when given to younger children (4,9). In our case the patient was 16 month old when diagnosis was established. He in high risk group, so needed low dose of radiation.

Without chemotherapy the total dose radiation terapy patients between 1 and 3 years of age receive 7.200 rads to 9.000rads. (6,9,14,16) And using adjuvant chemoteraphy the total dose radiation reduced to 4.500rads. (3,16,21) In our case the total radiation dose was 4.500rads.

In the region of whole brain received 3.000rads and 1.500rads prophylactically to the spinal cord.

The treatment was delivered over a total of 6 weeks in fractions of 100-200rads per day, 5 days per week.

With lowering radiation dose will increasing risk for tumour recurrance, for this reason, attention is being increasingly paid to the use of chemotherapy in this disease. (19,13)

In our case irradiation gave or 20 days post operation. usually irradiation give within 2 to 4 weeks after operation. (15)

The side effect of irradiation has mention before. The seriour effect are intellectual deferioration, endocinopathies. (4,5)

So far in our patient the intelligent appearance still in normal limit. But to ascertain need intellectual assessment.

Duffner (1985) suggested intellectual assessment should be done at least 1 year after the completion of irradiation.

About adjuvant chemotherapy, in our case Vincristine, Metotrexate and Dexamethasone had been given.

Vincristine has widely use to treat of pediatric cancer such as Hodgkin, ALL, Wilm's tumor. This agent produces much less bone-marrow depression and can be given to Leukopenic patients. (18,20) Vincristine is considered the most efficacious drug for medulloblastoma. (18) Many centers use this agent to treat medulloblastoma alone or in combination. (6,8,9,13,14)

Methotrexate is one of metabolites agent, its cytotoxic effect on neoplastic cells. (18,20)

In our case MTX in combination with Dexamethason gave intrathecaly for prevention of tumor dissemination.

Other chemotherapy commonly use to treat medulloblastoma are CCCNU, BCNU, Cisplatin, but these drug not available in Indonesia. Vinsristine was given at weekly intervals during radiotherapy. The courses being cycled every 6 weeks for a total of eight courses. (13)

In our case Vincristine gave at weekly during radiation therapy and maintenance cycled every 4 weeks for a total of 6 courses.

The chemotherapeutic using in Europe and United States included Vincristine, nitrosoureas, intrathecal MTX and hydrocortisone, and cyclophosphamite. (8) In our case for intrathecal used MTX and Dexamethasone.

The use of chemotherapy coupled with Radiation therapy and aggressive surgical resaction has resulted in encouraging over all 5 year disease free survival rates for patients with medulloblastoma.

But further follow up still needed for evaluation side effect of the treatment or tumor recurrence.

So far in our patient from cerebrospinal fluid evaluation and CT-scan after the operation there are not tumor recurrence or side effect of the treatment.

SUMMARY

A case of medulloblastoma in 16 month old boy has been reported. The clinical symptoms and sign, diagnostic and treatment were discused. The patient discharge with good condition.

There are no evidence of side effect of the treatment and tumor recurrence, attention is being increasingly paid to the follow up in more time.

REFERENCES :

1. Flores LE, Williams DL, Bell BA, O'Brien M, Ragab AH. Delay in the Diagnosis of Pediatric Brain Tumors. AJDC 1986; 140 : 684 - 686.

2. Graus F, Walker RW, Allen JC. Brain Metastases in Children. J. Pediatr 1983; 103 : 558 - 561.

3. Ahmed SR, Shalet SM, Compbell RHA, Deakin DP. Primary Gonadal damage following treatment of brain tumors in childhood. J.Pediatr, 1983; 103 : 562 - 565.

4. Duffner PK, Cohen ME, Thomas RM, Lansky SB. The Long-Term Effects of Cranial Irradiation on the Central Nervous System. Cancer 1985; 56 : 1841 - 1846.

5. Duffner PK, Cohen ME, Voorhess ML, Mac Gillivray MH, Bracher ML, Panahan A, Gilani BB. Long-Term Effects of Cranial Irradiation on Endocrine Function in Children with Brain Tumors. Cancer 1985; 56 : 2189 - 2193.

6. Hughes EN, Shillito J, Sallen SE. Medulloblastoma at the Joint for Radiation Therapy Between 1968 and 1984 : The Influence of radiation dose on the Patterns of Failure and Survival. Cancer 1988; 61 : 1992 - 1998.

7. Packer RJ, Sutton LN, Rorke LB, Littman PA. Prognostic Importance of Celular differentiation in medulloblastoma of childhood. J.Neurosurg. 1984; 61 : 296 - 301.

16. Packer RJ et al. Improved survival with the use of adjuvant chemotherapy in the treatment of Medulloblastoma. J. Neurosurg. 1991; 74 : 433 - 440.

17. Haslan RHA. Brain tumors in children. In : Behrman RE eds. Textbook of Pediatrics, 14th ed. Philadelphia : WB Saunders, 1992 : 1531 - 1538.

18. Monfardini S, Brumer K, Crowther D, Olive D. Manual of Cancer Therapy. 3rd ed. Geneva : UICC, 1981 : 39 - 55.

19. Miller JH, Fishman LS. Brain Tumors. In : Miller JH, White L. eds. Imaging on Pediatric Oncology. London : Williams & Wilkins 1985 : 57 - 94.

20. Moskowitz PS, Parker BR. Complications of Cancer Therapy. In Miller JH, White L eds. Imaging in Pediatric Oncology. London : Williams & Wilkins 1985 : 472 - 499.

21. Passat J. Tumor Otak, Presentasi Kasus, Naskah Lengkap Pendidikan Tambahan Berkala Ilmu Kesehatan Anak, Jakarta, 1989 : 271 - 276.

22. Jones PG, Campbell PE. Tumours of Infancy and Childhood. Oxfort : Balck well Scientific Publications, 1976 : 245 - 250.

23. Cohen ME, Duffner PK. Brain tumors in children 1st eds New York : Raven Press, 1984 : 232 - 244.