Management of Disseminated Neuroblastoma

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Very few children with disseminated neuroblastoma are cured, and spontaneous regressions are rare. This poor prognosis has not improved despite the combined use of surgery, radiotherapy and multiple chemotherapy alone or in combination. It should be emphasized, however, that only surgery and radiotherapy have been employed to their maximum potential. While chemotherapy has proven equally disappointing, it has been used at what may be considered sub-optimal time intervals and dosages.

The relatively good prognosis for infants under one year of age has biased the approach of some investigative oncologists who doggedly extrapolate successful treatment methods in the infant to the older child. By the time the tumor is diagnosed in the older child, it has survived a vicissitude of structural, biochemical and immune insults and, by selection, has become imbued with all the characteristics essential to its growth in a hostile environment. It may as well have managed to alter and thereby cohabit within its host. One cannot expect that neuroblastoma in an older child will disappear entirely simply by removing or radiating bits of tumor. Only by affecting each tumor cell can we hope to cure the patient. A more aggressive approach is thus required, involving maximum but safe utilization of chemotherapeutic agents and supportive measures for ending cytotoxicity. Recently, this approach has been pursued in the management of the child with neuroblastoma.

The Referral

The physician who suspects or has diagnosed neuroblastoma in a child has the responsibility of selecting one of the following options:

(A) to refer the child to a specialized cancer center;
(B) to retain the child outside the cancer center;
(C) to treat the child collaboratively with a regional center or treatment group, according to their contemporary treatment policy.

The decision is often based on geographical or financial factors, as well as the physician's previous association with cancer treatment groups or centers. In urban regions, many children with neuroblastoma are retained at their primary hospital under the assumption that

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the patient would be of teaching interest and because it is believed that he can be effectively managed locally. In contrast, suburban hospitals that often lack the personnel and resources of radiation therapy, pediatric chemotherapy and pediatric surgery have a greater tendency to refer these children to cancer centers.

Children in cancer centers are usually the subject of intensive study and are likely to be treated with new investigational drugs or unusual combinations. Therefore, the management of patients varies depending on their physical location and, once in the center, the availability of personnel capable of delivering uncommon or new combinations of drugs, as well as the amount of research support for patients’ expenses over long periods.

This review emphasizes the use of intensive chemotherapy in short courses for pediatric neuroblastoma patients in our cancer center. Clinical data on this regimen, although preliminary, are encouraging.

Principles of Management

- The location and extent of tumor dictates the magnitude and method of treatment, for example, surgery, chemotherapy, radiotherapy.
- The age of the patient may restrict the magnitude of chemotherapy. Patients over 15 and under one year of age are generally treated less aggressively, in the absence of extensive metastatic disease.
- The duration of treatment is a function of the method utilized. Surgery or radiotherapy are obviously short-term; chemotherapy is continued as long as two years when feasible.
- Chemotherapy involves an intensive induction phase of five to eight months, during which time the maximum amount is administered, with a maintenance phase of 15 months once gross tumor is eliminated.
- Biochemical serum and urine tests are used to monitor the patient’s course.
- A second-look exploration is valuable in certain specific situations.
- Close follow-up after successful therapy is mandatory for 20 years or more.

Diagnosis

The usual presenting signs and symptoms include: discovery of a mass (45 percent of cases); neurologic signs or inability to walk (20 percent); bone pain and limp (20 percent); orbital ecchymosis and/or proptosis (12 percent). The remaining three percent of patients have a variety of unusual complaints.
### Table 1.
Situations at Diagnosis
Requiring Urgent Treatment

|   | Description                                                                 |
|---|-----------------------------------------------------------------------------|
| A | Rapidly expanding retroglobal (orbital) tumor with proptosis.               |
| B | Extradural-intracranial extension of tumor with signs and symptoms of intracranial hypertension. |
| C | Extradural extension of tumor causing symptoms of cord compression.         |
| D | Thoracic mass with respiratory embarrassment.                              |
| E | Abdominal tumor resulting in intestinal or urinary tract obstruction.       |
| F | Severe anemia due to bone marrow replacement.                               |

Fig. 1. Clump of neuroblastoma cells found in bone marrow aspiration.
Minimal diagnostic studies should include radiographic skeletal surveys, intravenous pyelography, bone marrow aspiration, and 24-hour urinary vanillylmandelic acid (VMA), catecholamine and cystathionine content. Additional information concerning the total body burden of tumor can be obtained from isotopic scanning of bone with fluorine-18 or 99mTc pertechnetate, and of soft tissues with 67Ga citrate. Brain scans or myelography in the absence of neurologic signs add little diagnostic information. The diagnosis is most often, but not always, confirmed by histologic examination of biopsied or excised tumor. When extensive disease is present, elevated urinary VMA and catecholamines, and extrinsic cells in bone marrow aspirates (bone marrow biopsy has not proven to be of additional value) have been accepted for diagnostic pur-
poses. The majority of patients with bone lesions and tumor cells on bone marrow aspiration (Fig. 1.) survive only a short period, and the histologic diagnosis can be confirmed at autopsy.

**Treatment Options**

The clinical presentation usually determines the urgency and selection of treatment. (Table 1.) Although these findings reflect the location of the tumor, the extent of disease is often underestimated and all patients require further extensive investigation.

If the patient has a rapidly expanding retroglobal tumor with proptosis (Fig. 2.) or extradural-intracranial extension producing signs and symptoms of intracranial hypertension, treatment options include:

(A) Curative radiation to the involved orbit(s); when tumor(s) is nonradioresponsive and rapid growth occurs, ablation of the eye. Since all orbital tumors are metastatic, search for the primary and institution of systemic chemotherapy is required in addition to, and sometimes following, radiotherapy. There is little danger of administering chemotherapy shortly after or concomitant with radiotherapy since the field of radiation is limited.

(B) Alternative treatment (investigative): multiple drug regimen (N-3) as outlined in chemotherapy section (see page 272). When growth is arrested within one week of chemotherapy, radiation can be withheld. In the absence of objective signs of tumor regression, radiation therapy is required as in the above section.

If the patient has extradural extension causing symptoms of cord compression (Fig. 3.), following myelography and
localization, treatment involves:

(A) steroids and laminectomy with surgical decompression;
(B) steroids and radiation to an area extending above and below the involved region;
(C) either of the above followed by chemotherapy.

Many of these tumors have intrathoracic or intra-abdominal extensions or both, and tumor tissue remains within the intervertebral foramen. Consequently, complete surgical excision is improbable, and epidural tumors should be followed by careful study or surgical exploration of the intrathoracic and/or abdominal paravertebral regions.

If the patient has a thoracic mass or an abdominal tumor with intestinal or urinary tract obstruction, removal of tumor mass or diversion of the intestines or the urinary tract is the treatment of choice.

Surgery

Since tissue diagnosis is required in most cases, it is appropriate to first consider the role of surgery.

Total Removal of Tumor

Unfortunately, because of referral patterns, there is little opportunity for surgeons to totally remove the tumor. Surgical ablation was possible in only two of 250 patients at Memorial Sloan-Kettering Cancer Center. In both of these patients, the primary tumors were in the neck, and both patients are free of disease for 13 and 20 years respectively.

Surgical exploration should include a cytologic examination of ascites, if present, or a saline wash of the peritoneal cavity before and after surgery. Although uncommon, we have observed malignant ascites and transperitoneal metastases. (Fig. 4.) A study of peritoneal washings in children with neuroblastoma has been useful in determining prognosis, and should be repeated at any subsequent laparotomy. In all cases, the area from the diaphragm to the pelvis should be visualized and explored for tumor.

Abdominal tumors may arise from the adrenal medulla or the paravertebral sympathetic chain. Although the primary adrenal tumor may be removed with relative ease, most infants or children will have contiguous spread to the liver or kidney, lymphatic spread to the diaphragm, adjacent paravertebral and peripancreatic lymph nodes, or hematopoietic spread to the liver and bone marrow.

Following preoperative evaluation of serum electrolytes, uric acid and urinary function, it is advisable to remove as much of the primary adrenal tumor as possible, and to clip the borders of unresectable tumor for later radiographic examination or as guides to radiotherapy portals.

The paravertebral tumors are usually extensive. Although not necessarily bulky, they generally interdigitate between the renal hilum and the inferior vena cava and often involve the paravertebral lymphatics from the diaphragm to the pelvis. Extensive unresectable paravertebral disease is best handled by simple biopsy and by locating the borders of the neuroblastoma with silver clips.

During abdominal exploration, a wedge biopsy of the liver may be valuable in detecting microscopic hepatic metastases. To avoid confusion between an acute abdomen secondary to tumor growth and obstruction, and a potential inflammatory appendicitis, elective appendectomy at the time of exploration should be performed. Metastatic involvement of the appendix is rare (Fig. 4.), as is involvement of the intestine itself. (Fig. 5.) More commonly found is contiguous extension into the intestinal wall from adjacent involved lymphatics or tumor.

The Elective Second-Look Operation

This maneuver is usually applicable to patients who have only undergone
biopsy, and is based on the observation that some neuroblastomas are sensitive to treatment and may actually diminish in size permitting more complete resection. Neuroblastoma has been observed on rare occasions to convert to ganglioneuroma, although this is not usually how a tumor regresses. Up until the use of the regimen described in this article, it has been unusual to find evidence of histological conversions to ganglioneuroma in older children with a history of metastatic disease. Hence, exploration should be undertaken under stringent conditions which include evidence of systemic tumor arrest, as well as local reduction of tumor mass. In the absence of sufficient data at this time, maximally tolerated doses of drug, even with supportive measures, are given cyclically for a restricted period of time (five to eight months) at the end of which, re-exploration may be considered. This operative procedure may be of great utility in gauging further requirements for chemotherapy; histologic evidence of conversion can be used to modify both drug selection and further dose schedules.

The Surgical Specimen

In the past it has been common practice to simply send the surgical specimen to the pathology department for a routine histologic section and light microscopic study. Recent observation of a variety of immunologic and biochemical differences among neuroblastomas indicates that the tumor from a primary resection should undergo additional scru-
tiny, and that fresh tissues should be quick frozen and stored between −20°C and −80°C. These can later be studied for their biochemical characteristics including dopamine-B-hydroxylase (DBH), tyrosine hydroxylase, tryptophan hydroxylase, cyclic AMP phosphodiesterase, or choline acetyltransferase content, and used to prepare antigens for eventual immunologic studies.

When research facilities are available, fresh tumor should be utilized to establish in vitro permanent cell cultures. It can now also be transplanted into the "nude" mouse.2

Radiotherapy

The indications for radiotherapy in life-threatening conditions or in the presence of impending neurologic damage have already been described. Although there is incontrovertible evidence that radiotherapy is of value in the palliative management of the child with metastatic neuroblastoma, it alone, or given in combination with previously described chemotherapy programs, has not altered the cure rate.3 Because of most recent results in this investigative setting using a combination of drugs at maximally tolerated doses, radiation therapy is not now considered as part of the primary management of patients with disseminated disease. Exceptions include those

Fig. 7. Patient K.C.: (See p. 276) Intravenous pyelogram showing displacement of the left kidney by a paravertebral neuroblastoma.

Fig. 8. Patient K.C.: Biopsy of metastatic lymph node in the neck showing replacement by neuroblastoma tumor.
previously described emergency situations or experimental chemotherapy resistance. As more data are accumulated concerning the full range of effectiveness of this chemotherapeutic regimen, the potential application of combined radiation and chemotherapy may again be considered.

Chemotherapy

No rationale for a successful chemotherapeutic program for neuroblastoma can be established without recognizing certain considerations:

- The age of the host appears to play an important role in the curability, but not responsiveness, of the tumor. For example, using the same combination of drugs, the cure rate of children under two years old at diagnosis is about 50 percent; the cure rate in older children is zero to five percent.

- Resistance to chemotherapeutic agents develops very rapidly. The “natural history” of children treated with chemotherapy is partial or apparent complete tumor reduction for a few months, followed by return of disease, with a mean survival of eight to 10 months. In many programs, agents are given in moderate or low doses in a weekly or alternate weekly fashion. This probably leads to early drug resistance and treatment failure. In vitro observations of cultured neuroblastoma cell lines from patients revealed that each cell line consisted of a population of cells showing variations in resistance to different drugs, and varied biochemical characteristics. A presumed mechanism of drug resistance is centered on alterations in the ability of the tumor cell to transport the drug across its membranes. This is probably the mechanism by which drug resistant clones of neuroblastoma cells can be developed in vitro and an analogous phenomenon probably occurs in the patient with neuroblastoma.

- Some neuroblastomas have a tendency to convert to ganglioneuromas. This observation stimulated the use of vitamin B12 as a “maturation agent,” which was eventually shown to be ineffective in children with metastatic disease. Substances (dibutyryl cyclic AMP, sodium butyrate, papaverine) known to cause morphologic differentiation of murine and human neuroblastoma cells in vitro have had few clinical trials.

- In vitro studies with human neuroblastoma cells revealed that some agents are simply cytotoxic (daunomycin, vincristine), while others inhibit growth, reduce tumorigenicity and stimulate morphological changes suggesting maturation (F3TdR, papaverine, sodium butyrate, dibutyryl cyclic AMP). Therefore, the choice of drugs has to include cytotoxic as well as “maturation-inducing” agents. This should stimulate cells not killed by cytotoxic agents to undergo “maturation.”

- The natural selection of a resistant tumor has been alluded to, as well as the assumption that the tumor may somehow affect its host. An additional clinical requirement would be to “establish” those host factors present in the infant which make him so much more prone to cure than the older patient. It is fashionable to assume that deficiencies in the immune system are partly responsible for these differences. Unfortunately, the therapeutic capability of manipulating the immune system to repair such assumed deficiencies is not as yet established. Investigative programs using immune stimulators such as BCG, Bordetella pertussis vaccine and Levamisole are actually in progress for adults with cancer and eventually may lead to use in pediatric patients.

In light of these observations, it appears that any effective program should be designed to deliver the maximally tolerated amounts of drug within the
shortest period of time (four-day course every three to four weeks). This would theoretically deliver the maximum amount of drug to the tumor tissue and eliminate resistant tumor selection based on, in part, the membrane transport of anticancer agents.

**Current Program**

Our current program includes the use of four drugs which have shown some antitumor effect in previous clinical studies of individuals with neuroblastoma. Cyclophosphamide has been utilized in many patients. When used alone in a variety of schedules but in conventional doses (10-40 mg./kg.), an overall response rate of 40 percent occurs. The present program is unique in that the maximally tolerated dose of cyclophosphamide is used. In the past, these dosages have been generally limited to pretreatment of bone marrow transplant recipients. Since acute cardiac necrosis has been reported in one patient who received cyclophosphamide, 220 mg./kg. in four days, the use of 160 mg./kg., administered over a two- or three-day period as a maximum dose, was elected.

Nausea and vomiting following 20 to 80 mg./kg./day of cyclophosphamide can be limited by pretreatment with antiemetics, diuretics and adequate fluid intake. The magnitude of bone marrow toxicity as manifested by a delayed recovery of the white blood cell count is only slightly increased with the use of 160 versus 40 mg./kg. of cyclophosphamide. Compared to conventional drug doses, the higher serum levels obtained may be particularly advantageous when the normally sluggish blood flow within the bone marrow acts as a sanctuary for tumor cells. In order to diminish the renal and bladder toxicity of cyclophosphamide, excess intravenous fluid is given on the day of administration, and a diuretic (furosemide) is given prior to and following injection of the drug.

In previous clinical trials, vincristine caused beneficial responses in 22 percent of patients. Tri-fluoro-methyl-2-deoxyuridine was effective in two of six patients with widely disseminated neuroblastoma, and in the laboratory caused human neuroblastoma cells to undergo rapid morphological differentiation. Papaverine was recently found to inhibit tumor growth and cause temporary regression in four of eight patients with disseminated neuroblastoma; these patients were resistant to all conventional and some experimental agents. The average maximally tolerated dosage of 45 mg./kg. as a 12-hour infusion was established. This is eight times the usually accepted dosage for children, but is the amount which produces serum levels equal to or greater than those concentrations killing neuroblastoma cells in vitro.

Studies of the effects of papaverine on human neuroblastoma cells in our laboratory indicated that in addition to its anti-phosphodiesterase activity, it inter-
ferred with membrane transport of thymidine and sugars. This membrane transport inhibitory effect suggested that papaverine should be used following, rather than preceding or concomitant with, the administration of other anti-cancer drugs.

Such observations led us to construct the regimen shown at right. Four drugs are given intravenously in sequence and constitute a course. Courses are repeated every three to four weeks depending on recovery from bone marrow toxicity determined by measuring the peripheral blood count.

Careful attention is given to the patient’s cardiac and renal functions. If electrocardiographic changes of left ventricular hypertrophy develop during therapy, the patient is treated with digitalis. Patients are always placed on an electrocardiographic monitor during papaverine infusion. Each chemotherapeutic course generally results in a five- to ten-day period of bone marrow hypoplasia during which the patient may require transfusions of blood or platelets, and is particularly susceptible to infection. The reticulocyte count always drops to zero. Since the recovery of the reticulocyte count anticipates the return of hematopoietic function, it can be used to detect early recovery of the bone mar-

**Cyclophosphamide**
40-80 mg./kg.
(a) 10 a.m. on days #1, 2
(3 optional)

**Vincristine**
0.03 mg./kg.
(a) 10 p.m. on days #1, 2

**F3TdT**
20-45 mg./kg.
(a) 9 a.m. on days #3, 4

**Papaverine**
45 mg./kg.
(a) 10 a.m. to 10 p.m.
infusion on days #3, 4

Fig. 10. Patient K.C.: Repeat biopsy of metastatic lymph nodes in the neck three months later.
row, thereby avoiding unnecessary blood transfusions.

For all dose ranges the median hemoglobin, white blood cell count and platelet nadirs occur on day eight. Recovery of the white blood cell count ranges between three and 19 days with a median of eight days. (Fig. 6.)

Case History
Patient K.C. (Table 2.) had extensive metastatic spread to her mediastinum and neck from an abdominal primary. (Fig. 7.) Biopsy of the neck revealed metastatic neuroblastoma. (Fig. 8.) After treatment with the N-3 chemotherapy regimen, intravenous pyelography showed improvement (Fig. 9.), and repeat biopsy of a greatly diminished and more firm node taken from the site of the original biopsy showed ganglioneuroma and some neuroblastoma cells. (Fig. 10.) Part of this node was placed into tissue culture from which only fibroblasts grew, and an additional portion of the second biopsy was injected into three “nude” mice. After four months, no evidence of tumor growth in the culture or in the “nude” mice occurred. This suggested that the residual neuroblastoma cells lost their tumorigenicity. The patient continues to have no clinical evidence of disease 10 months after the beginning of anti-cancer drug therapy.

Fig. 11. Patient K.C.: Hematologic toxicity and changes in urinary VMA and catecholamines during treatment with combination chemotherapy (N-3) for neuroblastoma. The first course was administered while the patient was receiving total parenteral nutrition to determine if it would have any effect on the duration of bone marrow toxicity.
Table 2. Effects of Combination Chemotherapy (N-3) on Disseminated Neuroblastoma

| Patient | Age (year) | Previous Therapy | Location of Metastases at Onset of N-3 | No. Courses | No. Episodes | Response (See Table 3.) | Comments |
|---------|------------|------------------|----------------------------------------|-------------|-------------|-------------------------|----------|
| A.B.    | 1          | + VCR Cy Dact MeCCNU | Bone; Bone marrow; Soft tissue         | 8           | 1           | 1A*                     | Bone fractures healed, VMA and catecholamines normalized; died of varicella. |
| L.K.    | 2          | + VCR Cy Dact MeCCNU | Soft tissue                            | 3           | 3           | 0B*                     | Intractable diarrhea led to electrolyte imbalance and death; VMA and catecholamines normal; autopsy: tumor changed to ganglioneuroma. |
| R.C.    | 4          | + VCR Cy Dact MeCCNU | Bone marrow; Soft tissue               | 6           | 2           | 1A*                     | VMA and catecholamines decreased but abnormally elevated; re-exploration revealed ganglioneuroma. |
| R.P.    | 10         | + VCR Cy Adr DTIC   | Bone; Bone marrow; Soft tissue         | 6           | 1           | 1A*                     | Bone pain disappeared after 1st course; bone healing after 1 month; VMA and catecholamines normal. |
| D.L.    | 6          | + VCR Cy Adr DTIC   | Bone; Bone marrow; Soft tissue         | 1           | 1           | 1A*                     | Skull metastases decreased in size; bone pain and extrinsic cells disappeared 1 week after therapy. |
| M.S.    | 4          | - VCR Cy           | Bone                                   | 3           | 2           | 1A*                     | Repeat biopsy of rib — no evidence of tumor; VMA and catecholamines normal. |
| M.F.    | 5          | - VCR Cy Adr       | Bone; Bone marrow; Soft tissue         | 2           | -           | 1A*                     | Skull metastases decreased in size after 1st course; VMA and catecholamines normal. |
| K.C.    | 6          | -                  | Bone marrow; Soft tissue               | 6           | 2           | 1A*                     | Repeat biopsy of metastatic neck node — ganglioneuroma; VMA and catecholamines normal. |
| A.C.    | 3          | -                  | Bone; Bone marrow; Soft tissue         | 3           | -           | 1A*                     | Bone lesion healing; abdominal tumor greatly diminished; VMA and catecholamines normal; one episode of pseudomonas aerugino-sepsis. |
| M.D.    | 13         | -                  | Bone; Bone marrow; Soft tissue         | 1           | -           | 1A*                     | Bone pain disappeared after 1st course. |

1Patients L.K., M.S. and M.D. had a primary tumor which was ganglioneuroblastoma. The urinary VMA and catecholamines were elevated in all but M.D. at the beginning of therapy.

2All patients had some microscopic hematuria for 1–2 days following cyclophosphamide; gross hematuria was also ephemeral and the incidence diminished by simultaneous administration of intravenous fluids and diuretics.

3EPS — extrapyramidal motor symptoms following papaverine infusion.
Table 3. Categories of Response

| Category | Description |
|----------|-------------|
| O – A*  | Subjective benefit without favorable objective changes. |
| O – B*  | Favorable objective changes without subjective benefit. |
| O – C   | Subjective benefit and favorable objective changes in measurable criteria — less than one month. |
| 1A      | Distinct subjective benefits and favorable objective changes in all measurable criteria for one month or more. |

*Categories apply as long as improvement from baseline persists. Superscript time in months of duration of response. In patients with neuroblastoma the reduction in urinary vanillylmandelic acid and/or catecholamines is included as a favorable objective change. Evidence of reduction is necessary to achieve a 1A response in all patients with pretreatment elevated values.

Current Clinical Status

Eight of 10 patients who have been treated with this regimen are surviving. (Table 2.) Significant clinical responses were obtained in all patients. (Table 3.)

The small number of patients and limited duration of the study forestall any conclusions regarding the long-term efficacy of this regimen. However, if the status of the patients (only three were untreated), the good objective responses (three with evidence of conversion to ganglioneuroma, two with healing of pathologic fractures), the toxicity and increased susceptibility to infection, are balanced against a heretofore bleak prognosis, this experimental regimen may prove effective.

This article concerns the current investigative management (which may be subject to further modification) of neuroblastoma patients at Memorial Sloan-Kettering, and solely reflects the opinions of the author, and the accord of Dr. Murphy, Head, Department of Pediatrics, and the Clinical Investigation Committee.

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