Contemporary Treatment of Neuroblastoma: Single-Institution Experience from 10 Years

Sakari WIKSTRÖM and Ulla M. SAARINEN

Neuroblastoma is a malignant tumour of neural crest origin. The biological behaviour of neuroblastoma is fascinating and presents many enigmatic features. In the adrenal glands of fetuses and infants younger than 3 months of age dying of unrelated disease, incidental cellular in situ foci, histologically indistinguishable from nueroblastoma, have been reported to be relatively common findings [2,13]. Undoubtedly, most of these lesions never progress to clinical cancer. In addition, a symptomatic, clinical tumour may undergo spontaneous maturation and differentiation to a ganglionneuroblastoma or a definitely benign ganglionneuroma, or even regress spontaneously.

Neuroblastoma may arise at any site in the sympathetic nervous system, including the adrenal medulla and the sympathetic ganglia in the neck, mediastinum, retroperitoneal paraspinal region and pelvis. Patient age, the extent of the disease and primary tumour site strongly influence the likelihood of survival [6,7,11]. Infants under one year of age and children irrespective of age with stage I or II disease have usually a favourable prognosis, as have those with a primary tumour arising in the neck, mediastinum and pelvis [12]. In addition, tumour histology [23] and several biological markers like DNA ploidy, HVA/VMA ratio, serum ferritin, LDH and neuron-specific enolase (NSE) levels and particularly copy number of the N-myc oncogene are prognostic factors for patients with neuroblastoma.

Unfortunately, the majority of the patients present with an advanced abdominal primary tumour in association with metastatic disease, unfavourable histology and other known ill-favoured features (patient age over one year, DNA diploidy, amplification of the N-myc oncogene, a high HVA/VMA ratio, high ferritin, NSE and LDH levels), and the results of treatment in these cases have remained uniformly poor until recently. The dismal outlook seems, however, to be gradually improving after the introduction of bone marrow transplantation (BMT) allowing intensified cytoreductive treatment with or without supralethal total body irradiation (TBI) [1,10,17,18,19,22]. We report here our experience and results since 1981 when aggressive treatment of patients with neuroblastoma, also including BMT when indicated, was initiated at our centre.

Patients and Methods

Patients

Between May 1981 and December 1991, a total of 53 new cases of neuroblastoma were treated at the Children's Hospital, University of Helsinki, Finland. Patient age ranged from newborn to 14.9 years. Twenty-two patients (42 %) were less than one year old and 31 (58 %) were older. There were 35 males and 18 females (M/F ratio 2:1). The extent of the disease, classified according to the Evans' staging system (Table 1), is presented in Table 2 by site of the primary tumour. The most common primary site was within the abdomen in 42 cases (79 %), either in the adrenal medulla, 27 cases (51 %), or in the paraspinal sympathetic ganglia, 15 cases (28 %). Two massive abdominal tumours extended in continuity above the diaphragm. Thirty-six patients (68 %) presented with distant metastases.

Diagnostic evaluation

The initial diagnostic work-up consisted of abdominal ultrasound, chest x-ray, CT-scan, skeletal survey, technetium (99m Tc) bone scan, since 1984

Table 1. Evans staging system for neuroblastoma

Stage I	**Tumor** confined to the organ or structure of origin.
Stage II	**Tumor** extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.
Stage III	**Tumors** extending in continuity beyond the midline. Regional lymph nodes bilaterally may be involved.
Stage IV	**Remote** disease involving bone, parenchymatous organs, soft tissues or distant lymph node groups, or bone marrow.
Stage IV-S	**Patients** who would otherwise be Stage I or II but who have remote disease confined to one or more of the following sites: liver, skin, or bone marrow (without evidence of bone metastases).

MIBG-scan and bone marrow aspiration plus biopsy. HVA and VMA were measured in 24-h urine. The ultimate diagnosis was based on histological examination of tissue specimens, usually of the primary tumour obtained by surgery. In one infant presenting with a stage IV tumour, histological diagnosis was primarily made from a cervical lymph node metastasis and in two other infants with stage IV-S disease from the bone marrow aspirate. The tumours were histologically graded using the Shimada classification [23]. Immunohistochemistry included studies for neurofilaments and cell-surface disialoganglioside (GD2). The diagnosis and severity of the disease were further substantiated by a number of special investigations, including karyotype analysis from samples of tumour and bone marrow, and levels of serum ferritin and NSE. Since 1987 the presence and amplification of the N-myc oncogene in the tumour has been an integral part of the diagnostic protocol.

Operative staging consisted of an assessment of primary tumour margins including possible extension to the surrounding tissues, a sampling of regional lymph nodes and of suspected juxta-regional and distant nodes, the presence or absence of liver metastases, the feasibility of complete tumour resection, and, in initially unresectable tumours, of biopsy specimens of adequate size for histological confirmation and grading, as well as for the different special examinations. Based on the information obtained from histological examination of tumour specimens and the special investigations, the cases were classified as either good risk or poor risk tumours, and were treated accordingly. Poor risk cases were **1)** all patients with stage IV and older than 1 year at the diagnosis, **2)** all with N-myc amplification, irrespective of age and stage, **3)** those with stage III and unfavourable histology, older than 1 year at diagnosis.

Treatment strategy

All patients with stage I and all except one with stage II disease were considered to have a good risk tumour and required only complete surgical excision. In patients with good risk stage III disease, three cycles of COD (Cyclophosphamide 750 mg/m^2 on day 1, Vincristine 1.5 mg/m^2 on day 5, DTIC 250 mg/m^2 on days 1 to 5), repeated every 3 weeks, were given after resection or debulking of the primary tumour. In three out of a total of four cases in this subgroup, the tumour bed was treated with low-dose irridation (1 Gy) postoperatively. In addition, three of the patients needed second-look surgery to eradicate residual tumour. There were only two patients, both less than one year old, with a good risk stage IV tumour. Their chemotherapy consisted of COD supplemented with a weekly dose of VP-16 100 mg/m^2. Both patients underwent debulking of the primary tumour. One of the two needed a second-look laparotomy for residual abdominal disease.

The treatment of patients with stage IV-S neuroblastoma was variable. Nine out of 10 underwent removal of the adrenal tumour by adrenalectomy at some point of time. In three bilateral cases, biopsy or tumour enucleation of the less involved side preserving the adrenal was performed simultaneously. One neonate died within three weeks from complications of compression caused by the massively enlarged metastatic liver before any attempts at surgery. Up-front or somewhat delayed surgery was performed in 7 cases. In two most recent cases, adrenalectomy was postponed to the ages of 3.3 and 4.2 years, recpectively. Four patients received no other treatment except surgery. Six earliest patients were treated with cytoreductive treatment consisting of Cyclophosphamide and Vincrisine, supplemented with VP-16 in two cases. In two patients the enlarged liver was treated with low-dose irradiation. Two patients eventually underwent the BMT protocol I (see below), one for nonresponding pro-

Table 2. Stage of the tumour by primary site at diagnosis in 53 patients with neuroblastoma

Primary tumour			Stage				
Site	N	%	I	II	III	IV	IV-S
Neck	4	8	2	2	-	-	-
Mediastinum	7	13	2	2	1	2	-
Adrenal medulla	27	51	-	2	-	15	10
Retroperitoneum	15	28	-	-	6	9	-
Total	53	100	4	6	7	26	10

gressive disease causing life-threatening complications and the other for a massive recurrence 8 months after diagnosis.

Two different treatment protocols were used for poor risk tumours. Patients admitted between 1981 and 1985 were treated according to protocol I and the subsequent cases using protocol II.

Protocol I. There were two stage III and 13 stage IV tumours. All except one of the patients had an abdominal primary. One had a mediastinal stage IV tumour. Treatment commenced with surgery. In nine patients the procedure was biopsy only. In six patients primary tumour resection or debulking was performed. Twelve patients needed a second-look operation, and six of these a third-look laparotomy. Cisplatinum 50-100 mg/m^2 on day 1 and VP-16 75-100 mg/m^2 on days 1 to 3 were administered with intervals of 2 to 4 weeks for induction therapy, in total of 6-10 courses. Consolidation therapy consisted of a single dose of Melphalan 140-180 mg/m^2, followed by autologous bone marrow transplantation (ABMT), harvested just before administration of the drug, and given back fresh and unfrozen. One patient died of progressive disease during induction therapy. A second ABMT was performed in two patients for tumour relapse. One of the two was treated, in addition, with total body irradiation (TBI, 10 Gy).

Protocol II. There were altogether 13 poor risk patients, one with stage II, one with stage III and unfavourable histology, and 11 with stage IV tumours. One stage IV tumour was of mediastinal origin; all the others were abdominal primaries. The patient with stage II disease was the only case in the entire patient population presenting with unfavourable tumour markers including amplification of the N-myc oncogene, but diagnosed before the age of one year. Chemotherapy commenced with 2-4 cycles of COD every 3 weeks to shrink the tumour and to clean the bone marrow. If there was no response to COD, the schedule was changed to 2-3 cycles of Adriamycin 30 mg/m^2 on days 1 and 2, and Cisplatinum 90 mg/m^2 on day 1. Surgery for the primary tumour was undertaken either initially or at some time during the chemotherapy, when considered operable. A second-look tumour resection or debulking was performed when necessary.

Low-dose irradiation was given to local tumour residuals, while also additional chemotherapy, consisting of a weekly dose of Vincristine 1.5 mg/m^2 and Cyclophosphamide 400 mg/m^2 of 2 weeks, was administered. Second-look laparotomies were performed in seven cases and a third-look operation once. The preparative regimen was "VMP+TBI": day -9 VP-16 150 mg/m^2, day -8 Cisplatinum 90 mg/m^2, day -7 VP-16 150 mg/m^2, day -6 rest, day -5 Melphalan 140 mg/m^2, day -4 Melphalan 70 mg/m^2, days -3 to -1 TBI of 10 Gy in 3 to 5 fractions. Ten patients were treated by autologous BMT and one patient received an allogeneic marrow graft from a HLA-matched sibling. Two patients were never autografted because of rapidly progressing non-responding disease. One patient was treated with a double ABMT program, receiving high-dose Thiotepa on the second round.

Purging. No attempt was made to remove any potential neuroblastoma cells from the bone marrow inoculum. We applied "in vivo" purging by the chemotherapy given to the patients. The bone marrow was repeatedly checked for the presence of tumour cells by immunological methods using the anti-GD2 monoclonal antibody 3A7, with a de-

Table 3. Progression-free survival of 53 patients with neuroblastoma by stage of tumour

Stage	Survival				
		2 years		3 years	
	N	N	%	N	%
I good risk	4	4	100	4	100
II good risk	5	5	100	5	100
II poor risk	1	0	0	0	0
III good risk	4	3*	75	3	75
III poor risk	3	3	100	3	100
IV good risk	2	2	100	2	100
IV poor risk	24	13	54	11**	46
IV-S	10	9***	90	9	90
Total	53	39	74	37	70

** one death due to interstitial pneumonitis, NED,*
*** one relapse after 2.9 years, death due to progressive disease; another death after 2.5 years of post-radiation restrictive respiratory insufficiency, NED,*
**** one neonatal death due to respiratory, cardiovascular and urinary complications caused by compression of enlarged liver.*

tection limit of 1:50,000 [3,20]. When the marrow was clean, it was harvested, frozen and cryopreserved in liquid nitrogen until used.

Results

The outcome of the patients by tumour stage is presented in Table 3. The overall 3-year survival rate was 70 %. In the good risk tumour group (stages I to IV) 14 out of a total of 15 patients (93 %) survive. One toxic death was due to interstitial pneumonitis; no tumour was detected at autopsy. The outcome was equally good among the patients with stage IV-S disease; 9 out of 10 patients (90 %) survive. The only death was caused by secondary consequences of metastatic liver compression in a neonate. Two patients with stage IV-S disease still have multiple subcutaneous nodules consisting of benign ganglionneuromatous tissue.

The poor risk group comprised altogether 28 patients, of whom 16 (57 %) survived at 2 years and 14 (50 %) at 3 years after diagnosis. In disseminated disease, comprising 24 patients, the corresponding 2 and 3 year survival rates were 54 % and 46 %, respectively.

The only stage II poor risk patient died of widely disseminated disease 1.2 years from diagnosis and 6 months post-ABMT, despite such favourable factors as young age and a low initial tumour stage. On the other hand, all three patients with a stage III poor risk tumour survived. All presented with an advanced abdominal tumour. Two patients needed two laparotomies to eradicate the primary, and the third patient needed extensive surgery consisting of a laparotomy, followed 3 weeks later by a dorsal laminectomy to remove a sizeable spinal extension of the tumour.

The results for patients with stage IV poor risk neuroblastoma using the two different treatment protocols were as follows: Five out of 13 patients on protocol I died within 24 months. Four patients died of uncontrollable tumour and one of septicaemia during post-Melphalan pancytopenia. Induction therapy failed in two patients. One of the two was autografted despite of only partial remission. Two late relapses occurred among protocol I patients, though only one had a fatal outcome. The other patient had an abdominal recurrence 5 years after diagnosis. The extirpated tumour appeared to be a mature ganglionneuroma but the patient received conventional chemotherapy and radiotherapy, and is well with no evidence of disease 10 years after initial diagnosis. In summary, 7 out of 13 patients with a stage IV tumour (54 %) survive after a follow-up period ranging from 9.8 to 13.5 years after diagnosis.

Six out of the 11 stage IV poor risk patients on protocol II died within 24 months. Five deaths were due to uncontrollable or recurrent tumour; two of these patients were never grafted. One patient treated by allogeneic BMT died posttransplant 1 year after initial diagnosis of acute GVHR and septicaemia without any evidence of tumour. Another patient died 2.5 years after diagnosis of progressing restrictive pulmonary failure, free of tumour. Four out of the 11 patients (36 %) survive after a follow-up period of 4.0 to 8.3 years. Of the 8 autografted patients, 4 (50 %) survive.

A second ABMT, performed in three patients, two on protocol I and one on protocol II, was in none of the cases of benefit. The two patients on protocol I died of septicaemia during the posttransplant period, though with no evidence of neuroblastoma at autopsy. The third patient treated with a double transplant program was well and with stable disease for 9 months, but died of disease progression 11 months after the second ABMT.

Survival by primary tumour site among the stage IV poor risk cases was 2/2 (100 %) in the mediastinal tumours, 5/15 (33 %) in the abdominal tu-

mours, when of adrenal origin, and 4/7 (57 %) in extra-adrenal retroperitoneal disease. Five out of 9 (56 %) of patients in whom ipsilateral nephrectomy had been performed to ensure radical tumour margins, survive. One of these patients lost the remaining kidney for resistant fungal growth. The patient is living well and disease-free 4.3 years after diagnosis and 1.7 years after a successful kidney transplant.

To be noted, all patients with an extra-abdominal, i.e. cervical or mediastinal tumour, survive irrespective of the severity of their disease.

Discussion

Historically, the most important determinants of improved survival in neuroblastoma have been considered to be a patient age of less than one year, stage I, II or IV-S disease, and a primary tumour site in the neck, mediastinum or pelvis. This concept obviously holds true in most cases, and is also supported by our results. There are, however, several biological tumour markers available at present, which enable more accurate and specific identification of those patient subgroups who have unfavourable prognosis. Chromosomal changes, most importantly the amplification of the N-myc oncogene, but also the 1q deletions, seem to indicate a dismal outlook. A high HVA/VMA ratio, high serum ferritin, LDH and NSE levels, and unfavourable tumor histology are poor prognostic factors, as well.

On the other hand, good risk and favourable outcome is associated with favourable histology in stage III, and age less than one year in stage IV, provided that only a single copy of the N-myc oncogene is present. The outcome of our 15 good risk tumour patients appeared, in fact, to be hampered solely by one treatment related complication. The major future consideration in these patients will, hence, be the avoidance of unnecessary chemotherapy causing both short-term and late toxicity, as well as of unnecessary radiotherapy, which may be followed by life-long disabling physical consequences and an increased risk of secondary malignant neoplasms arising in the irradiated region. Undoubtedly, stage IV good risk patients (=infants) and stage III good risk patients, particularly those with gross incomplete resection of the tumour, need gentle or moderate chemotherapy. In stage I-II patients with a completely resectable localized tumour, surgery alone is an adequate mode of treatment.

The treatment of infants with stage IV-S disease is more controversial. The majority of the patients survive without any therapy except, perhaps, excision of the primary lesion. The existing problem is in identifying the few infants who will develop either life-threatening complications due to tumour compression, or progressive or recurrent disease. These patients present rarely with unfavourable features, although N-myc amplification has appeared as a poor prognostic factor also in stage IV-S neuroblastoma. When the decision is made, only to observe the child, close observation is essential until regression and/or maturation of the tumour occurs. The use of a temporary silastic silo to make room for the enlarged liver by creating an artificial ventral hernia has been proposed [8]. We have not applied the technique in neuroblastoma, but our experience using the silo in the treatment of gastroschisis has been disappointing. Local radiotherapy is one modality advocated for a massive metastatic liver; in young infants, we would like to prefer chemotherapy, and have obtained encouraging responses by a single dose of cyclophosphamide. In two complicated cases we used high-dose chemotherapy with marrow rescue with good results. We are not sure whether the two patients were overtreated.

In striking contrast to the excellent outlook of the good risk tumour subgroups, the results of treatment of patients with poor risk neuroblastoma are still far from satisfactory. Of our 53 patients 28 (53 %) presented with a poor risk tumour and only 14 (50 %) survive. The introduction in the early 1980's of supralethal chemotherapy with or without TBI with marrow rescue has unquestionably changed the outlook of the patients with an advanced poor risk neuroblastoma from hopeless to hopeful, but at present, the results are only modest. Less than half of the patients with disseminated disease survive even in the best series [14,15,16,24,25] despite of presumed improvements in chemotherapy, designed by numerous multicentre trials in Europe, Japan and the United States. Among our patients there was no difference in long-term outcome between the two treatment protocols for poor risk tumours. The small group sizes and sequential study design do not allow further comparisons.

The effect of more aggressive surgery has been

intensively investigated. For poor risk stage III, improved survival rates after complete resection of the primary tumour have been reported [14,25]. The results of surgery in disseminated disease have, however, been controversial. According to the CCG report [14] resectability of the primary tumour at delayed surgery did not affect survival in stage IV, and the authors concluded, that resolution of metastases by chemotherapy is more important than surgery. On the contrary, the Japanese study group [25] reported that patients with gross complete resection in stage IV had a better prognosis than those with partial resection, whether operated primarily or later. They also reported that patients in whom the ipsilateral kidney was preserved at surgery had an outcome superior to that of those with associated nephrectomy. In our experience, an aggressive surgical approach is of benefit in both stage III and stage IV disease. Second-look and even third-look operations seem to be justified for primary tumour residuals.

Ipsilateral nephrectomy to ensure the radicality of the operation had no adverse effect on ultimate outcome of our patients, contrary to the Japanese [25] experience.

Future considerations. Possible future approaches might include new, more effective cell-cycle oriented chemotherapy regimens that activate the tumour cell from the resting to a proliferative phase where it would be more sensitive to chemotherapy and irradiation [12], post-BMT biotherapy with cytokines, monoclonal antibodies and differentiation inducers for minimal residual disease [5,21], and gene manipulation therapy. So far the conclusions from the first clinical trials have been cautious [4,9] but more promising results will undoubtedly soon become available.

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Sakari Wikström, MD
Department of Pediatric Urology
Children's Hospital University of Helsinki