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The Treatment of Advanced Neuroblastoma. Results of the Spanish Neuroblastoma Study Group (SNSG) Studies

V. Castel, P. García-Miguel, C. Melero, A. Navajas, S. Navarro, J. Molina, M.D. Badal and J.I. Ruiz-Jimenez on behalf of the Spanish Neuroblastoma Study Group

The Spanish Neuroblastoma Study Group has conducted a study on advanced neuroblastoma (N-I-87), which included 33 stage III and 60 stage IV neuroblastoma children more than 1 year of age , enrolled between October 1987 and April 1992. They were staged according to Evans and treated with induction chemotherapy (IC) consisting of 3 courses of cyclophosphamide–doxorubicin alternating with 3 of high-dose cisplatin–teniposide. Evaluation after IC and surgery demonstrated an overall response rate of 88% for stage III and 69% for stage IV. In the latter, complete responses and good partial responses were 33 and 14%, respectively. After surgery, children received maintenance chemotherapy (all stage III except 2 and 30 stage IV) or autologous bone marrow transplantation (ABMT) (11 stage IV), the distribution was not randomised. Probability of survival at 5 years was 0.60 ± 0.12 for stage III and 0.24 ± 0.07 for stage IV. A significant difference in survival at 5 years was found between "good responders" and "non-responders" to initial chemotherapy.

Keywords: neuroblastoma, stage III neuroblastoma, stage IV neuroblastoma, ABMT
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INTRODUCTION

THE SPANISH Neuroblastoma Study Group began its activities in 1987. A central secretariat, pathology review and, since 1991, a central biology laboratory are the main facilities of the group. Their activities have been developed in different areas including:

(i) providing the Spanish Society of Paediatric Oncology with diagnostic and therapeutic protocols, which are followed by most of the Spanish hospitals;
(ii) providing a system of quality control of the neuroblastoma cases registered; and
(iii) performing clinical and biological research.

Children, up to 16 years of age, diagnosed as having neuroblastoma, have been registered and treated in different studies depending on their age and stage. A study has been conducted on advanced stage neuroblastoma in children older than 1 year. The N-I-87 trial was opened in October 1987, closed in June 1992, and updated results are summarised in this paper. The main aims of the study were to reduce the tumour mass by chemotherapy, allowing extensive, or even complete, resection of stage III tumours; to avoid organ resections and mortality due to surgical complications; and to reduce the use of radiotherapy.

Correspondence to V. Castel.
V. Castel is at the Pediatric Oncology Unit, Hospital Infantil, La Fe, Valencia, P. García-Miguel is at La Paz, Madrid; A. Navajas is at Cruces, Bilbao; C. Melero is at 12 de Octubre, Madrid; J. Molina is at Virgen del Camino, Pamplona: S. Navarro is at the Department of Pathology, Hospital Clínico, Valencia; M.D. Badal is at the Radiotherapy Hospital, La Fe, Valencia: and J.I. Ruiz-Jimenez is at the Pediatric Surgery Hospital, Virgen de la Arrixaca, Murcia, Spain.

PATIENTS AND METHODS

Children older than 1 but up to 16 years of age and previously untreated were enrolled in the N-I-87 study. Disease extent was assessed by means of ultrasonography, computed tomography or magnetic resonance imaging, [$^{123/131}$I]MIBG (meta-iodobenzylguanidine) scan, bone marrow aspiration and biochemical markers (urinary catecholamine metabolites, neuron specific enolase (NSE) and ferritin).

Disease extent was classified according to Evans [1]. Response to treatment was considered a complete response (CR), good partial response (GPR), partial response (PR), stable disease (SD) or progressive disease (PD) [2], and was evaluated after induction chemotherapy, and again after surgery. The severity of toxicity was graded according to World Health Organisation criteria [3], and ototoxicity was evaluated according to the Brock's system for bilateral hearing loss [4]. Children with stage III or IV neuroblastoma were treated with the same induction chemotherapy (IC) consisting of 3 courses of cyclophosphamide–doxorubicin alternating with 3 courses of high-dose cisplatin–teniposide (Figure 1) followed by surgery. Resectability was decided in each case by the local surgeon. The administration of chemotherapy was encouraged as a first step, after confirmation of diagnosis, followed by surgical treatment.

Results of surgery were described according to the postsurgical TNM system for neuroblastoma [5]. Operative and postoperat-

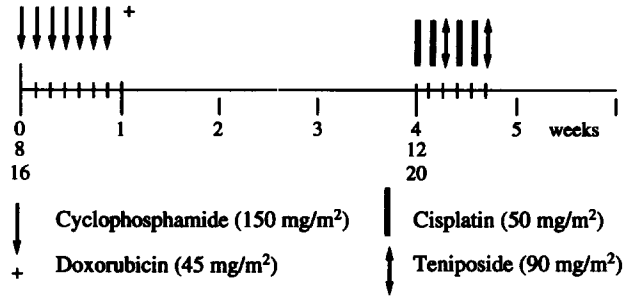

Figure 1. Induction chemotherapy for Stage III and IV neuroblastoma in children >1 year old.

ive complications were carefully noted. In cases where the biopsy was the initial surgical procedure, second-look surgery was always attempted unless clinical complete response was obtained after chemotherapy, or clear disease progression was demonstrated.

Radio therapy was only administered to patients with macroscopic residual tumour after chemotherapy and surgery. Maintenance chemotherapy (Figure 2) was administered to most stage III patients for 1 year; stage IV patients were treated by either autologous bone marrow transplantation (ABMT) or maintenance chemotherapy, but were not randomised.

194 children were registered, but only 93 were older than 1 year with advanced stage, 33 with stage III and 60 with stage IV.

Statistical analysis

The probability of survival (S) and event-free survival (EFS) was calculated from the time of diagnosis according to the Kaplan and Meier product-limit method with standard errors of Peto. All survival curves were evaluated at 5 years. In the survival analysis, deaths for any reason were considered events. In the EFS analysis, disease progression, relapses and deaths for any reason were also considered events. Survival curves in different subgroups were compared by means of the Mantle-Haenszel χ^2 test. Comparisons between proportions were performed using Fisher's exact test with 95% confidence interval. The P values were two-tailed.

RESULTS

Stage III

Of the 33 patients with stage III disease, resection was initially attempted in 13 patients, but in all cases resection was incomplete, with microscopic residual tumour (PT3A) remaining in 7 patients and macroscopic tumour (PT3B) in 6. Of the 20 patients whose tumours were considered inoperable at diagnosis, 17 underwent second-look surgery after chemotherapy. No tumour was found in 2 patients, complete resection was possible in 6, microscopic residual tumour remained in 3 and macroscopic residual disease remained in 6. 3 patients were not operated on after chemotherapy because of PD. All patients received induction chemotherapy, either after surgical resection (n = 13) or after biopsy (n = 20). Of the 33 patients, 32 had completed therapy at the time of this analysis and were evaluable for response. The combination of IC and surgery produced CR in 15 children (47%), GPR in 7 (22%), PR in 6 (19%), SD in 1 (3%) and PD in 3 (9%) (Table 1).

Toxicity caused by IC was mainly haematological followed by otic and renal, and was considered severe in 8 children. There were 4 episodes of infection. 2 children failed to complete IC, 1 because of anaphylaxis with teniposide and the other because of serious otic toxicity. There were no toxicity-related deaths.

Apart from 3 nephrectomies, no other organ excision was performed. The number of surgical complications (3/46 surgical interventions, excluding biopsies), was very low, comparing favourably with other published series [6, 7].

Radiotherapy was administered exclusively to 5 patients with macroscopic residual tumour after IC and surgery.

The 3 patients with PD received no further treatment. 27 children received maintenance chemotherapy (MC) and 2 ABMT. MC was well tolerated; mainly haematological toxicity was present in 11 patients and was serious in 4. 2 children died in CR (sepsis and vascular accident). 8 patients relapsed (at 9, 12, 14, 18, 21, 30, 30 and 31 months after diagnosis), 4 with regional spread and 4 with distant metastases, and died. Currently, 19 children are alive, 18 free of disease and 1 with a residual stable tumour. Median survival is 60 months (range 32 to 79 months). All are off therapy. Actuarial survival (Figure 3) and event-free survival (EFS) at 60 months were 0.60 ± 0.12.

Bilateral high frequency hearing loss occurred in 5 survivors. The audiometric results have not been modified in repeated studies. Hearing aids are not being used by any of the children, but one needs special help at school.

Creatinine clearance is normal in all survivors, but 9 have high levels of magnesuria, and are continuing treatment with oral magnesium supplements.

Stage IV

Of the 60 patients, 58 were evaluable for response, with 2 chemotherapy-related deaths (see below). The overall response rate to induction chemotherapy in the 58 patients was 69%. The CR and VGPR were 33% and 14%, respectively, following

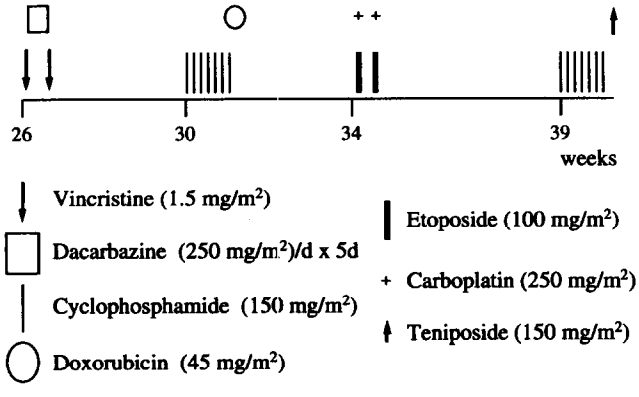

Figure 2. Maintenance chemotherapy. The complete course was repeated 4 times.

Table 1. Response evaluation in 32 stage III patients submitted to induction chemotherapy and surgery

	No.	%	
CR	15	47	(88%)
GPR	7	22	
PR	6	19	
SD	1	3	
PD	3	9	

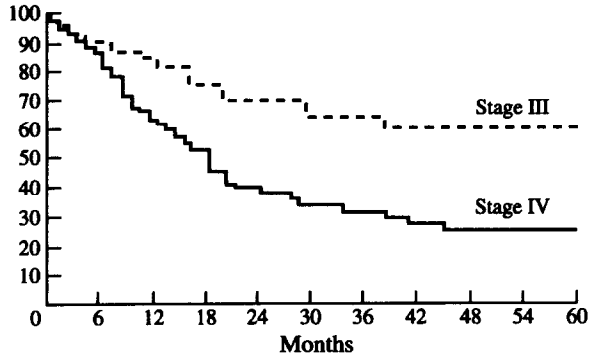

Figure 3. Actuarial survival stages III and IV >1 year old.

surgery (Table 2). PD occurred during or at the end of induction chemotherapy in 22% of patients.

Metastasis disappeared after chemotherapy in 33 patients (57%), although the organs involved increased in 6 (10%). The least responsive were bone metastases. Toxicity from induction chemotherapy occurred in 38 patients, grade 3–4 in 11. There were two chemotherapy-related deaths, one from sepsis and the other from acute renal failure. 43 patients underwent surgery and 17 patients did not receive surgery (2 unknown primary, 11 PD, 2 SD, 2 toxic complications). Complete excision was performed in 13, no residual tumour was found in 1, microscopic residual tumour remained in 10 and macroscopic residual tumour in 19. Histological examination of the tumours after chemotherapy revealed that 20 were neuroblastoma, 19 were ganglioneuroblastoma, 2 were ganglioneuroma and in 2 only fibrosis was found.

Children attaining CR, GPR or PR were treated by maintenance chemotherapy (MC) (30 children) or ABMT (11 patients). 9 patients received local irradiation (35 Gy) for gross residual disease.

46 patients died 25 days to 47 months after diagnosis (mean survival time 15.5 months); the causes of death in 4 cases were sepsis, acute renal failure, haemorrhagic and surgical complications and the remaining 42 because of PD. 14 children are alive and disease-free, 33–74 months from diagnosis (mean survival 55 months).

The probability of survival of the entire group at 60 months was 0.24 ± 0.07 (Figure 3) and EFS was 0.19 ± 0.06. Median survival was 26 months.

The probability of survival at 5 years for patients with CR was 0.35 ± 0.14, with GPR 0.50 ± 0.20, with PR 0.32 ± 0.18; and with SD and PD 0.0. Differences were only statistically significant when comparing the "responders" (CR-VGPR-PR) with the "non responders" (SD-PD) $P < 0.001$. Median survival was 22 months for CR and GPR, 35 months for PR, 9 months for SD and 4.5 months for PD.

11 patients received ABMT. One patient died because of haemorrhagic complications, and 4 relapsed at 15, 15, 19 and 27 months from diagnosis. Survival at 5 years was 56% ± 26%. In the group of 30 children treated by MC, the disease progressed in 18, 7–47 months after diagnosis, and survival was 28% ± 10% (P = NS) (Figure 4).

DISCUSSION

Considering these and other published results [8–10], we would recommend a conservative surgical approach at diagnosis in children with stage III neuroblastoma, becoming more aggressive only in second-look procedures. Chemotherapy must be administered to all stage III tumours, after biopsy is performed, as very few are completely resectable at diagnosis. This procedure can avoid surgical complications and mortality. Other intensive but less toxic chemotherapy protocols might be considered in children with regionally advanced neuroblastoma.

For patients with stage IV neuroblastoma, the initial response rate (69%) was similar to that from other published studies [11–13], but considering that in 22% of the patients the disease progressed during the first 6 months, this is still poor. The probability of survival at 5 years (0.24) was comparable to the best published results [14–16] but nevertheless is poor. We found a significant difference in survival between responders and non responders. The children treated with ABMT had the best outcome, with survival at 5 years of 56%, although this should be treated with caution as the group was very small and selected for its initial response. Acute and long term toxicity were not negligible, and we intend to investigate other combinations of drugs in further studies.

A second study of children above the age of 1 year with advanced neuroblastoma was initiated in May 1992 and is ongoing. So far 15 stage 3 and 22 stage 4 (INSS and INRC classification) patients have been enrolled, and the overall response rate to induction chemotherapy and surgery is currently 85% for stage 4 patients. Toxicity is tolerable. These initial results are encouraging, but whether outcome will be affected remains to be seen, with more patients and longer follow-up required.

Table 2. Response of stage IV patients to chemotherapy (IC) (58 patients) and chemotherapy plus surgery (43 patients)

	I.C.		I.C. + surgery	
	No.	(%)	No.	(%)
CR	6	(10)	19	(33)
GPR	21	(36)	8	(14)
PR	13	(22)	13	(22)
SD	5	(9)	3	(5)
PD	13	(22)	–	

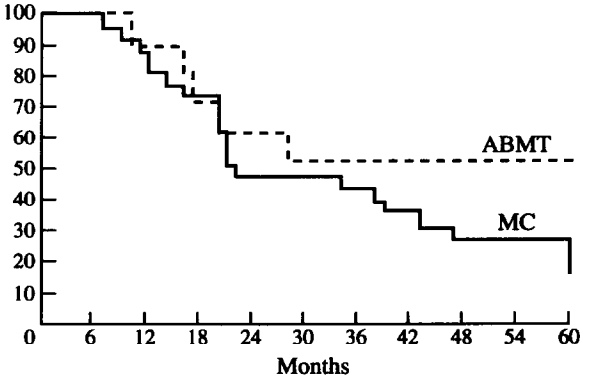

Figure 4. Survival stage IV >1 year.

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