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# First Experience with Prognostic Factors in Unselected Neuroblastoma Patients. The Austrian Neuroblastoma 87 Study

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**Between January 1987 and December 1993, 117 patients were registered in the Austrian A-NB87 study. The male/female ratio was 1.18, with 50 patients below the age of 1 year at diagnosis. Patients were assigned to stage according to the result of primary surgery in localised disease. Age, ferritin and neuron specific enolase were used in addition in stage III disease for risk-adapted treatment. Adrenal or pelvic primary tumour sites were mainly associated (81%) with advanced disease. The median observation time of the study is 3.5 years. The overall survival at 3 years was excellent in low stage disease and IVs patients, i.e. 100% for stage I and IIA (20 patients), 92% in stage IVs (13 patients), 81% in stage IIIA (18 patients) and 69% in stage IIB (8 patients). Stage IV (38 patients) showed a survival rate of 51%, whereas stage IIIB (10 patients) had the worst outcome in this study, i.e. 20%, due to treatment-related toxicity. Significant unfavourable prognostic factors were neuron specific enolase (NSE) > 100 ng/ml, ferritin > 300 μg/ml and amplified *MYCN*. This study achieved a better survival rate in stage IV patients and a subgroup of stage III in comparison to our previous study (*Pädiatrie und Pädologie* 1986, 21, 269) and gives the basis to further reduce treatment intensity in low-risk disease based on biological factors. However, prognosis for high-risk cases was still poor in spite of a very aggressive treatment concept.**

**Key words: neuroblastoma, prospective study, prognostic factors, neuron specific enolase, ferritin, age, *MYCN*, del 1p**

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## INTRODUCTION

NEUROBLASTOMA is the most common childhood solid tumour before the age of 5 years, with a prognosis closely related to disease extension and age at diagnosis [1–3]. In 30% of cases, it presents as localised disease (stage 1, 2, 3). The prognosis is generally good with survival rates ranging from 40 to 90%, and is influenced by the degree of local disease extension, the quality of surgical excision and biological factors that appear to have a major impact according to most recent observations [4–7]. In 5% of cases, neuroblastoma is observed in infants with a special disease pattern (stage 4s). Although they present with metastatic spread to liver, skin and bone marrow but no bone lesions, survival is more than 80% [4–8]. In contrast, 65% of neuroblastoma patients present with metastatic spread, most frequently involving the bone marrow and bones, and before the era of dose escalation strategies with or without bone marrow support, their prognosis was extremely poor, with a survival expectancy of less than 10% [9]. This has been improved to up to 50% event-free survival rates at 2 years during the last decade. However, long-term survival is still in the range of only 20–30% [10].

Since 1979, neuroblastoma patients were treated according to a common concept in Austria [11]. We report here our experience with our last protocol, the Austrian A-NB87 study, which used risk-adapted treatment intensity according to stage and age, and selected prospectively prognostic factors such as neuron specific enolase (NSE) [4, 12] and ferritin [4, 13] in stage III disease. In more recent years, biological factors such as *MYCN* amplification [14, 15] and 1p deletion (del 1p) [16] were also evaluated.

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## PATIENTS AND METHODS

### *Definition of stage and risk groups*

Disease was assessed by a full clinical assessment, evaluating before and after surgery, the extent or residue of the primary tumour by means of computer tomography and sonography, a chest X-ray, urinary catecholamine excretion, bone scan (99 Tc scan and/or meta-iodobenzylguanidine (MIBG) and bone marrow (2 aspirations and 2 biopsies). Patients were assigned to

*Table 1. Treatment plan A-NB87*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stage I | Sx only | | | | | | |
| Stage IIA | Sx | If macroscopic residual disease, second look surgery or local radiation (24–30 Gy) | | | | | |
| Stage IIB | Sx | VVVVVV<br>CCCCCC | | 2nd Sx or<br>Rx | | | |
| Stage IIIA | Bx or Sx | C1–C2 | C1–C2 | 2nd Sx | C1–C2 | Rx (C1–C2) | (3rd Sx) |
| Stage IIIB | Bx or Sx | C1–C2–C3 | C1–C2–C3 | 2nd Sx | C1–C2–C3 | Rx (C1–C2–C3) | (3rd Sx) |
| Stage IV | Bx | C2–C3 | C2–C3 | Sx<br>PBSC | C2–C3 C2–C3 | MGT +/− TBI<br>BM rescue<br>(auto or allo) | (Rx) |
| Stage IVS | If symptomatic, V or VC weekly | | | Sx of primary tumour at the best time | | | |

Bx, biopsy; Sx, surgery; Rx, radiation; C, cyclophosphamide; V, vincristine; C 1,2,3, cycle 1,2,3 (see Table 2); PBSC, peripheral blood stem cells, MGT, megatherapy; TBI, total body irradiation; BM, bone marrow; auto, autologous; allo, allogenic.

stage and risk groups according to the result of primary surgery in localised disease and age, ferritin and NSE in stage III disease.

In Stage I, the tumour was confined to the organ of origin and completely resected. In Stage IIA, the tumour extended beyond the organ or structure of origin, but did not cross the midline nor were regional lymph nodes involved; Stage IIB showed ipsilateral lymph node involvement. In Stage IIIA, the tumour extended across the midline and/or contra or bilateral lymph node involvement was present, and all of the following characteristics had to be present: age under 2 years, ferritin under 300 μg/ml and NSE under 100 ng/ml. In Stage IIIB, the definition for tumour extension was the same as for Stage IIIA, but at least one of the following characteristics was present: age over 2 years, ferritin over 300 μg/ml and NSE over 100 ng/ml. Stage IV was assigned if any distant metastases were identified such as bone marrow, skeleton, lymph nodes, soft tissues or other organs. Patients were considered as Stage IVs whenever age was under 1 year and distant metastases were found in the liver and/or skin and/or bone marrow, but not in the skeleton (skeleton X-ray survey and/or 99 Tc scan.)

*Patients*

Between January 1987 and December 1993, 117 patients were registered in the A-NB87 study from 10 institutions in Austria. The majority of patients were treated in Vienna (42%), 25% were from Graz, 10% from Innsbruck, 10% from Linz and 13% from different smaller hospitals. Only 107 patients of the population were eligible for analysis. 10 patients were excluded from the analysis for the following reasons: histology (ganglioneuroma in 5 patients), age over 20 (2 patients), one treatment refusal by parents, one patient had previous treatment outside the protocol and in one infant the diagnosis was just given on autopsy.

There were 49 girls and 58 boys. Fifty patients were infants, i.e. less than 1 year at diagnosis. The primary tumour site was identified in the cervical region in 6 patients, in the thorax in 15 patients, in the adrenal gland in 65 patients, in the retroperitoneum in 12 patients, in the pelvis in one patient, and finally 8 patients presented with dumbbell tumours. According to the definition of risk groups as outlined above, patients were assigned to stage: stage I, 11 patients; stage IIA, 9 patients; stage IIB, 8 patients; stage IIIA, 18 patients; stage IIIB, 10 patients; stage IV, 38 patients; and stage IVs, 13 patients. Suprarenal, retroperitoneal and pelvic primary tumour sites were predominantly (81%) observed with advanced stage, i.e. III or IV (66 patients). At the time of analysis (April 1994), the median observation time of the study was 3 years 6 months (range, 4 months–7 years 3 months).

*Treatment*

The treatment schedule in accordance with the defined risk groups is summarised in Table 1. Multi-agent chemotherapy was used in the following combinations. Either cyclophosphamide (CYC) and vincristine (VCR) or cycle 1 (DAMO), cycle 2 (MVDOC) or cycle 3 (IPE)—agents and dosages are summarised in Table 2. It has to be emphasised that any second look surgery and/or radiotherapy [17], as given in Table 1, was only indicated in case of residual tumour demonstrated at re-evaluation.

*Definition of response*

For definition of response, the international response criteria were applied as previously published [18].

*Bone marrow harvest*

A total of 20 bone marrow and/or peripheral stem cell re-infusions (17 autologous and 3 allogenic) were performed. All autologous bone marrows were analysed by cytology and purged with Asta-Z as previously described [19].

*Megatherapy regimens*

Various megatherapy regimens were used within this protocol for stage IV patients. Either L-phenylalanine mustard (melphalan: L-PAM: 120–180 mg/m$^2$) alone or in combination

*Table 2. Elements of chemotherapy*

| | Agents | Dose (mg/m$^2$) | Days |
|---|---|---|---|
| Cycle 1 | Dacarbazine | 850 | d1 |
| (DAMO) | Doxorubicin | 30 | d1 + d2 |
| | Mustargen | 6 | d1 |
| | Vincristine | 1.5 | d1 + d5 |
| Cycle 2 | Mustargen | 6 | d1 |
| (MVDOC) | Tenoposide | 150 | d1 |
| | Dacarbazine | 850 | d1 |
| | Vincristine | 1.5 | d1 |
| | Cyclophosphamide | 850 | d1 |
| Cycle 3 | Ifosfamide | 3000 | d1 + d2 |
| (IPE) | Cisplatin | 40 | d1–d5 |
| | Etoposide | 150 | d3–d5 |

with etoposide (VP16: 60 mg/kg) with or without total body irradiation (TBI: 1.5 Gy twice a day on 4 consecutive days, i.e. total dose 12 Gy with lung shielding). In more recent years, the combination of TBI (as outlined above), L-PAM (120–140 mg/m$^2$, VP16 (60 mg/kg) and carboplatin (CBDCA: 3 times 500 mg/m$^2$) was used [20].

*Statistical methods*

Probabilities of overall survival (OS) were analysed according to the Kaplan–Meier method and survival curves were compared using the log-rank test [21].

## RESULTS

As expected, 62% of the children presented with advanced disease at the time of diagnosis. i.e. 28/107 with stage III and 38/107 with stage IV. Unfavourable prognostic factors in this study, such as elevated NSE, ferritin, *MYCN* amplification and del 1p, were more frequently observed with advanced disease. The association between these factors and stage are detailed in Table 3. The whole study population eligible for analysis ($n$ = 107) achieved an OS of 67% at 3 years. OS results at 3 years according to sex, age, stage, ferritin, NSE, lactate dehydrogenase (LDH), *MYCN* and del 1p are summarised in Table 4, and are demonstrated for stage in Figure 1 and Table 5.

*Cause of death*

36 of 107 patients died; 21 died of their disease. However, 14 patients died with treatment-related complications. One stage IIB patient died of surgical bleeding, and one for another reason (accident). Overall, 13/28 stage III patients died and 8 were treatment-related deaths, with 3 patients having septicaemia, one with fungal infection (*Aspergillus*), one with respiratory syncitial viral pneumonia, one with acute organ toxicity and 2 died due to surgical complications. 20/38 stage IV patients died and 5 were treatment-related deaths, with 3 patients having multiple organ failures following megatherapy and bone marrow rescue, and 2 having septicaemia.

## DISCUSSION

The excellent outcome in stage I as well as in stage II patients without lymph node involvement has been previously reported [4]. In the A-NB87 study, results are in line with these reports, although at least some stage IIA patients (i.e. those with favourable prognostic factors) were probably overtreated if judged against current standards [5, 21], since they were scheduled for second look surgery and/or local irradiation in case of macroscopic residual disease after first surgery. No late effects have been reported so far for this group. Chemotherapy, given either alone or combined with radiation therapy, has been reported as highly effective in the remaining stage II patients (IIB), resulting in long-term survival in approximately 75% of cases [22, 23]. This expectation was also met by the A-NB87 treatment strategy.

Treatment of Stage IIIA tumours was one of the major aims of the study, evaluating the feasibility of a less aggressive treatment strategy in the very young patients with stage III disease, showing favourable NSE and ferritin levels at diagnosis. The overall survival probability of 83% confirms a favourable outcome in this group of neuroblastoma patients.

Patients with stage IIIB were supposed to improve their prognosis with intensification chemotherapy (cycle 3), but this goal was not achieved. Conversely, this group had the poorest outcome of all groups, with survival of only 20% due to a high treatment-related toxicity. 2 children died due to bleeding complications after surgery. One was an infant diagnosed by screening who died at initial surgery [24]. This emphasises the

*Table 3. Distribution of prognostic factors by stage*

| Prognostic factor | Number (nb) of patients (pts) | | | | | |
|---|---|---|---|---|---|---|
| | Stage I $n$ = 11 | Stage II $n$ = 17 | Stage III $n$ = 28 | Stage IV $n$ = 38 | Stage IVs $n$ = 13 | Total $n$ = 107 |
| NSE | | | | | | |
| < 100 mg/ml | 10 | 16 | 18 | 13 | 10 | 67 |
| ⩾ 100 ng/ml | 0 | 0 | 7 | 21 | 1 | 29 |
| Total nb of pts investigated | 10 | 16 | 25 | 34 | 11 | 96 |
| Ferritin | | | | | | |
| < 300 μg/ml | 9 | 15 | 24 | 23 | 8 | 79 |
| ⩾ 300 μg/ml | 0 | 1 | 3 | 12 | 4 | 20 |
| Total nb of pts investigated | 9 | 16 | 27 | 35 | 12 | 99 |
| LDH | | | | | | |
| Not elevated | 7 | 7 | 12 | 5 | 6 | 37 |
| Elevated: < 1 yr of age, > 400 U/l | 0 | 2 | 3 | 5 | 5 | 15 |
| > 1 yr of age, < 300 U/l | 0 | 6 | 7 | 23 | — | 36 |
| Total nb of pts investigated | 7 | 15 | 22 | 33 | 11 | 88 |
| *MYCN* | | | | | | |
| Not amplified | 4 | 7 | 7 | 11 | 3 | 32 |
| Amplified | 0 | 1 | 4 | 8 | 1 | 14 |
| Total nb of pts investigated | 4 | 8 | 11 | 19 | 4 | 46 |
| del 1p | | | | | | |
| Not present | 4 | 9 | 7 | 4 | 5 | 29 |
| Present | 0 | 1 | 0 | 10 | 1 | 12 |
| Total nb of pts investigated | 0 | 10 | 7 | 14 | 6 | 41 |

NSE, neuron specific enolase; LDH, lactate dehydrogenase.

*Table 4. Summary of the various factors tested for their influence on overall survival*

| | Number of patients | | | Overall survival at 3 years (%) | | | *P*-value |
|---|---|---|---|---|---|---|---|
| Age at diagnosis | | | | | | | |
| ≤ 1 year | | 50 | | | 80 | | |
| > 1 year | | 57 | | | 57 | | S |
| Sex | | | | | | | |
| Female | | 49 | | | 71 | | |
| Male | | 58 | | | 63 | | NS |
| Stage | All | ≤ 1 year of age | > 1 year of age | All | ≤ 1 year of age | > 1 year of age | |
| I, IIA | 20 | 10 | 10 | 100 | 100 | 100 | |
| IIB | 8 | 4 | 4 | 69 | 67 | 67 | NS |
| IIIA | 18 | 14 | 4 | 81 | 83 | 75 | NS |
| IIIB | 10 | 1 | 9 | 20 | 0 | 22 | S |
| IV | 38 | 30 | 8 | 51 | 47 | 53 | S |
| IVs | 13 | 13 | — | 92 | 92 | — | NS |
| NSE | | | | | | | |
| ≤ 100 ng/ml | | 67 | | | 80 | | |
| > 100 ng/ml | | 29 | | | 38 | | S |
| Ferritin | | | | | | | |
| ≤ 300 μg/ml | | 79 | | | 73 | | |
| > 300 μg/ml | | 20 | | | 44 | | S |
| LDH | | | | | | | |
| < 1 year of age | | | | | | | |
| ≤ 400 IU/ml | | 25 | | | 91 | | |
| > 400 IU/ml | | 15 | | | 79 | | NS |
| > 1 year of age | | | | | | | |
| ≤ 300 IU/ml | | 12 | | | 61 | | |
| > 300 IU/ml | | 36 | | | 40 | | NS |
| *MYCN* | | | | | | | |
| Not amplified | | 32 | | | 88 | | |
| Amplified | | 14 | | | 33 | | S |
| del 1p | | | | | | | |
| Not present | | 29 | | | 88 | | |
| Present | | 12 | | | 64 | | NS |

NSE, neuron specific enolase; LDH, lactate dehydrogenase; S, significant; NS, non significant.

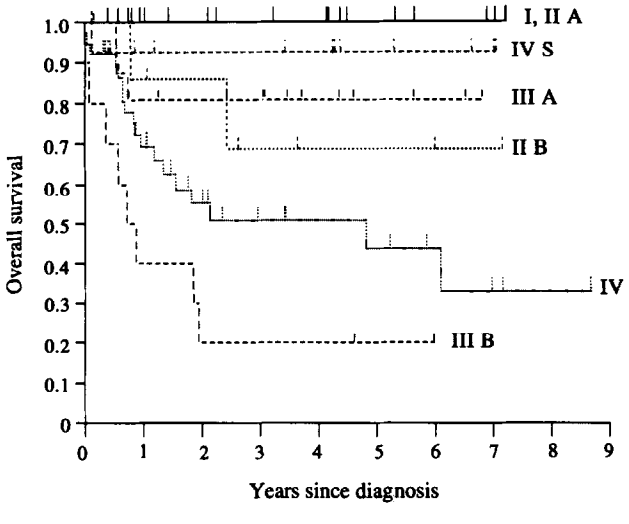


**Figure 1. Overall survival according to stage of disease.**

*Table 5. Overall survival according to stage of disease*

| Stage | Number of patients | Mean age ± S.D. (years) | Overall survival (%) |
|---|---|---|---|
| I, IIA | 20 | 1.90 ± 2.99 | 100 |
| IIB | 8 | 1.88 ± 2.90 | 69* |
| IIIA | 18 | 0.71 ± 0.39 | 81 |
| IIIB | 10 | 5.83 ± 5.08 | 20*† |
| IV | 38 | 3.36 ± 3.88 | 33* |
| IVS | 13 | 0.36 ± 0.25 | 92‡ |

* Significantly different from stage I, IIA; † Significantly different from Stage I, IIA, IIB as well as IIIA; ‡ Significantly different from Stage IIIB and Stage IV.

necessity of a careful pre-operative evaluation to decide the extent of the surgical intervention, and of discussing with the paediatric oncologist whether aggressive surgery is indicated or not.

The group of stage IV patients was heterogeneous. Various

megatherapy (MGT) regimens were used during the study period, and only 20 patients received MGT followed by bone marrow rescue. 4 patients entered a pilot protocol of repetitive single agent high dose chemotherapy without bone marrow support, the others either progressed and were not eligible for MGT or died of toxicity during induction. However, it appears that the more intense induction regimen and consolidation with MGT had an important impact on improvement (survival 51% at 3 years) in comparison to a previous study [1], with an overall survival of only 21.4% at 2 years.

The experience with stage IVs infants was favourable resulting in a 92% OS rate. Age at diagnosis with a cut-off point at 1 year was a significant prognostic factor, justifying a less aggressive treatment schedule in the infant group in the next protocol.

LDH [25, 26] did not have a significant impact on outcome in this study, whereas the role of NSE [4, 12] and ferritin [4, 13] as prognostic factors was confirmed with more than 90% of patients tested in the study. The correlation with biological paremeters such as *MYCN* amplification and 1p deletion is not clear from this study since biological parameters were not tested during the whole study period. So far, *MYCN* (46/107 tested) appears to have a significant impact on overall and event-free survival when all stages were amalgamated for analysis. However, the role concerning the various stages of disease cannot be demonstrated from this study since patient numbers are too small in the subgroups, and we have to rely on previous reports demonstrating the significant role in localised disease patients [6, 7]. One stage IIB patient with *MYCN* amplification and 1p deletion progressed. One stage IIIA patient showed amplification, but otherwise favourable criteria (age, NSE, ferritin) and is alive progression-free. 2 stage IIIB patients with amplification died, one with toxicity and one with progressing disease. One stage IVs patient with *MYCN* amplification was treated more intensively and is alive. Another IVs patient with 1p deletion showed rapid progression and died with disease. In stage IV disease, there appears no significant correlation between outcome and *MYCN* amplification and/or 1p deletion.

Thus the experience of the A-NB87 study can be summarised as follows. Good risk factors in this study were age under 1 year at diagnosis, low stage disease including stage I, II and IIIA but also stage IVs, normal NSE and ferritin levels, as well as absence of *MYCN* amplification. Outcome for patients with those characteristics was excellent, and suggests further reduction of treatment intensity to avoid short and long-term toxicity. Treatment-related toxicity was unacceptable in stage IIIB patients in this study and highlights the necessity of centralising patients whenever highly aggressive treatment concepts need to be applied. Overall survival for stage IV patients has been improved, although long-term prognosis still is disappointing. To further improve results, risk-adapted treatment intensity will be based on age and *MYCN* amplification at diagnosis in the new A-NB94 study.


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