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Tumour markers are poor predictors for relapse or progression in neuroblastoma

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Abstract

The value of the tumour markers vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine (u) and serum (s), neurone-specific enolase (NSE), and lactate dehydrogenase (LDH) in the early prediction of relapse/progression in neuroblastoma is not known. We analysed the data of neuroblastoma patients who had successfully completed first-line treatment and had laboratory results available from their initial diagnosis and from relapse/progression ($n=196$). Patients' overall survival from relapse or progression was 21.5±4.2% (mean±standard deviation). At diagnosis, we found abnormal results in 75% for VMA and/or HVA (s), 92% for VMA and/or HVA (u), 90% for NSE, and 81% for LDH. We found a lower incidence of abnormal results at relapse or progression with 40% for VMA and/or HVA (s), 54% for HVA and/or VMA (u), 61% for NSE, and 48% for LDH. Sensitivity of all markers was higher for metastatic compared with local recurrence. NSE was the best, being able to detect 42% of the localised relapses, 77% of the combined local/metastatic relapses, and 69% of the metastatic recurrences. Relapse or progression in neuroblastoma cannot be detected reliably by monitoring tumour markers alone. Therefore, follow-up of neuroblastoma patients must include clinical assessment and imaging studies.

Keywords: Neuroblastoma; Relapse; Tumour markers; Vanillylmandelic acid; Homovanillic acid; Neurone-specific enolase; Lactate dehydrogenase; Follow-up

1. Introduction

Vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels in serum (s) and urine (u) and the serum levels of neurone-specific enolase (NSE) and lactate dehydrogenase (LDH) are considered characteristic tumour markers of neuroblastoma. These parameters are well described at the initial diagnosis [1–3] and during the response assessment of neuroblastoma [4,5]. Therefore, tumour markers are commonly monitored in the follow-up of neuroblastoma survivors. However, the value of these markers in the early prediction of relapse or progression in neuroblastoma is not known. We analysed our data to learn more about the incidence of abnormal tumour markers at the time of progression or relapse of neuroblastoma.

2. Patients and methods

The data of 1764 consecutive patients of the Cooperative Neuroblastoma Treatment Trials NB90 and NB97 were reviewed retrospectively. All data were collected with the informed consent of the patients/parents. The initial diagnosis was established by histology, by typical bone marrow metastasis in combination with abnormal catecholamines according to the International Neuroblastoma Staging System (INSS) criteria [3], or in seriously ill children by typical tumour localisation with a distinct ^{123}I metaiodobenzylguanidine (MIBG) uptake in the tumour area and abnormal catecholamine levels. Relapse was defined as the reappearance of the primary

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tumour or metastasis, and progression was defined as the growth of residual disease [6] diagnosed by:

i. ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) in combination with abnormal tumour markers and/or
ii. distinct deterioration of MIBG scintigraphy and/or
iii reappearance or new bone marrow metastasis and/or
iv. histology after biopsy or resection of tumour.

Since we wanted to focus on the value of the measurement of tumour markers in the follow-up period, patients were included in the analysis only if the relapse or progression occurred after complete first-line treatment, stratified according the stage and risk profile:

i. Observation patients (NB90: stage 1 patients, NB97: stages 1 and 2 with minimal residual tumour and infants with stage 3 without dangerous symptoms): all recurrences,
ii. Standard-risk patients (NB90: stage 2 and stage 3 low-risk patients, NB97: children over 1 year of age with non-resectable stage 2 and stage 3 disease and infants with stages 1, 2 and 3 and dangerous symptoms): all recurrences after chemotherapy,
iii. High-risk patients (NB90: stage 4 and stage 3 high-risk patients, NB97: stage 4 and all patients with *MYCN* amplification): all recurrences after completion of induction chemotherapy, or after the start of maintenance treatment in NB90, or after the start of antibody treatment in NB97 (for details of therapy see Refs. [7,8]).

Patients were included in this analysis only if they underwent routine follow-up and if at least one tumour marker was available from the initial diagnosis, as well as from the recurrence confirmed as outlined. Since it is not clear whether tumour markers analysed more than one week prior to or one week after the diagnosis of recurrence are representative for recurrence, such results were excluded from the analysis. Therefore, some patients have results missing for some of the tumour markers because they were analysed earlier or later than 1 week.

VMA and HVA determinations were done by gas chromatography/mass spectroscopy in the laboratory of DHH [9] or in some cases in local laboratories. NSE blood levels were determined centrally by the Roche enzyme immunoassay or locally by the participating hospitals. The blood activity of LDH was measured by the local laboratory. For all parameters, age-related normal values from the literature or the local laboratory values were used [10,11].

Survival analysis was performed according to the Kaplan–Meier-estimation and log-rank test.

3. Results

Among 1764 patients, 77 patients (4.4%) were lost to follow-up. The median observation time of all surviving patients was 4.7 years (range 23 days–13.0 years). We observed a total of 506 relapses or progressions. 104 recurrences occurred during treatment and were excluded from this analysis. 402 recurrences occurred after complete initial treatment. Of these, 196 children were evaluable for this analysis having one or more tumour markers available from the initial diagnosis and from recurrence (±1 week). The remaining 206 patients had to be excluded due to missing data. This group of 206 patients contained more stage 4 patients (79%) than the 196 patients included in this analysis (66%, χ^2 $P = 0.013$), and the patients excluded from the analysis had a shorter survival from relapse/progression (1.4 years) than the evaluable 196 patients (1.6 years, Mann–Whitney-U-test $P < 0.001$).

All evaluable patients underwent routine follow-up as recommended in the trial protocol. Diagnosis of relapse/progression was established by ultrasound, CT or MRI and elevated tumour markers in 39 patients, by MIBG scintigraphy in 131 patients, and/or by the appearance or reappearance of bone marrow metastasis in 59 patients. Relapse or progression was confirmed by histology prior to any salvage treatment in 63 patients. For 138 patients, we had additional information as to why the assessment was done: only in 19 patients (14%) did routine assessment of tumour markers reveal abnormal results. In 61 patients (44%), relapse/progression was found by routine follow-up ultrasound, CT, MRI or MIBG scintigraphy, in 56 patients (41%) a relapse was suspected due to clinical symptoms, and in 2 patients (1%) an assessment was done for symptoms not related to the relapse.

The mean age of the patients at the initial diagnosis was 3.9 years (range 3 days–24.4 years). The mean time to relapse/progression was 1.7 years (range 0.1–6.6 years). 44 relapses and 23 progressions occurred after localised neuroblastoma and 79 relapses and 50 progressions after INSS stage 4 neuroblastoma (Table 1).

Overall survival of the 196 patients from the relapse or progression was 21.5±4.2% (mean±standard deviation). Fig. 1 shows the better prognosis of patients

Table 1
Stage distribution of 196 patients with relapse or progression of neuroblastoma

INSS Stage	Number of analysed patients	Number of relapses	Number of progressions
1	15	15	0
2	18	12	6
3	34	17	17
4	129	79	50
Total	196	123	73

INSS, International Neuroblastoma Staging System.

Table 2
Incidence of abnormal results at recurrence of disease compared with first diagnosis (for each parameter only patients with results available from the first diagnosis and recurrence are included)

Parameter	Initial		Relapse/progression	
	Number of abnormal results/number of assessed patients	% of abnormal results (sensitivity)	Number of abnormal results/ number of assessed patients	% of abnormal results (sensitivity)
VMA (s)	39/55	71	17/55	31
HVA (s)	40/55	73	20/55	36
VMA and/or HVA (s)	41/55	75	22/55	40
VMA (u)	71/87	82	44/87	51
HVA (u)	77/87	89	37/87	43
VMA and/or HVA (u)	80/87	92	47/87	54
NSE	97/108	90	66/108	61
LDH	64/79	81	38/79	48
Ultrasound/CT/MRI	145/146	99	109/146	75
MIBG Scintigraphy	117/121	97	114/121	94

VMA, vanillylmandelic acid; HVA, homovanillic acid; MRI, magnetic resonance imaging; CT, computed tomography; MIBG, ^{123}Imetaiodobenzylguanidine; LDH, lactate hehydrogenase; NSE, neurone-specific enolase.

with local relapse/progression after neuroblastoma stages 1–3 ($n=37$) compared with patients with local recurrence after stage 4 neuroblastoma ($n=18$), metastatic recurrence after localised disease ($n=30$), and metastatic recurrence after stage 4 disease ($n=111$; $P<0.01$).

Table 2 compares the incidence of abnormal results from first diagnosis and relapse/progression. Catecholamine results are given as the incidence of abnormal HVA, VMA, and the combination of HVA and/or VMA. In general, the combination yielded a higher sensitivity than the single results. Urinary catecholamine metabolites appeared more sensitive than serum results (sensitivity of 54% versus 40% at relapse or progression). LDH had a similar sensitivity (48% at relapse or progression). NSE had the highest sensitivity of all analysed tumour markers identifying 61% of the recurrent patients. Sensitivity of ultrasound, CT and MRI in recurrence was far higher detecting 75% of patients. A total of 94% of the relapsed/progressing patients had an abnormal MIBG scintigraphy either at the primary and/or metastatic site.

The sensitivity of tumour markers depended on the extent of recurrent disease (Table 3). In local relapse or progression, none of the tumour markers were able to detect many of the recurrent patients. In most patients, the diagnosis was established by ultrasound, CT, MRI, or MIBG scintigraphy. In metastatic recurrence of disease, urinary catecholamine metabolites and NSE were able to identify 60% or more of the patients. Ultrasound, CT, MRI and scintigraphy were positive in most of the local or combined local/metastatic recurrences. Nevertheless, none of these methods was able to detect 100% of patients.

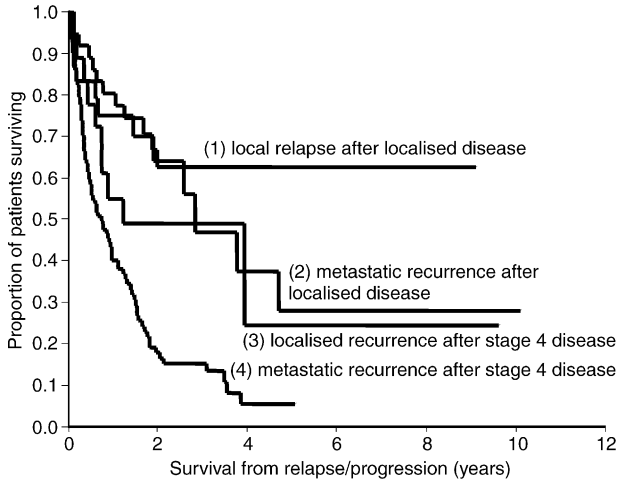

Fig. 1. Survival of 196 patients after relapse/progression ($P<0.01$): (1) local relapse after localised disease, $n=37$, 5-year-overall survival (OS) 62%±9%, (2) metastatic recurrence after localised disease, $n=30$, 5-year-OS 28%±13%, (3) localised recurrence after stage 4 disease, $n=18$, 5-year-OS 24%±18%, (4) metastatic recurrence after stage 4 disease, $n=111$, 5-year-OS 5%±3%.

Table 3
Incidence of abnormal tumour markers by extent of relapse or progression (All patients with results available from relapse/progression are included)

Parameter	Isolated local relapse	Combined local and metastatic relapse	Only metastatic relapse
Total number of patients	55	69	72
VMA and/or HVA (s)	3/17 (18%)	17/31 (55%)	9/30 (30%)
VMA and/or HVA (u)	8/35 (23%)	29/48 (60%)	34/52 (65%)
NSE	15/36 (42%)	33/43 (77%)	29/42 (69%)
LDH	10/23 (43%)	14/28 (50%)	15/30 (50%)
Ultrasound/CT/MRI	50/52 (96%)	44/52 (85%)	16/47 (34%)
MIBG scintigraphy	34/37 (92%)	52/53 (98%)	45/49 (92%)

4. Discussion

Tumour markers are widely used in the initial assessment of neuroblastoma patients. They are considered a good tool for the follow-up of neuroblastoma patients, but there has been no data which demonstrate their value for the follow-up of neuroblastoma survivors.

In our series, the sensitivity of the tumour markers in relapse or progression was found to be low. Many recurrences were diagnosed by routine ultrasound, MRI, MIBG scintigraphy, or when the patient became symptomatic. Only in 14% of patients did abnormal tumour markers in a clinically well patient lead to a further assessment which detected a relapse or a progression.

In general, tumour markers were more sensitive for the detection of metastatic relapse or progression. We found abnormal catecholamine metabolites in a few local relapses but in more than 50% of the metastatic relapses. Urinary catecholamines were always more sensitive than serum catecholamines. For localised recurrences, LDH and NSE had a similar sensitivity of around 40%. For metastatic recurrences, NSE was far better, detecting approximately 70% of patients, whereas LDH was able to detect only approximately 50%. This has previously been reported by Massaron and colleagues who found that NSE anticipates the clinical relapse in 21/52 (40%) patients and rises simultaneously with relapse in 29/51 (57%) patients [5]. The sensitivity of imaging studies was far higher. A high sensitivity of MIBG scintigraphy has been reported earlier by other authors in a small series of relapsing neuroblastoma patients [12,13]. Recently, Okuyama and colleagues observed abnormal tumour markers in only 3 of 8 recurrent neuroblastoma patients [13].

An important issue in assessing tumour markers is the specificity. We cannot give data on the specificity of these tumour markers because the study was restricted to relapsed/progressing patients and included no control group.

The prognosis of relapsed neuroblastoma is poor. The survival of these 196 selected patients according to the initial disease stage and extent of recurrence is given in Fig. 1. The plot is calculated from our patients who met the selection criteria outlined above and might be worse in unselected patients since rapidly progressing or seriously ill patients might have been excluded due to missing results. However, the figure gives an impression of the poor prognosis, particularly of metastatic relapse after complete treatment for stage 4 neuroblastoma. But even in this situation, survival of several months is possible.

To our knowledge, this is one of the largest series of relapsed neuroblastoma patients reported to date. The major problem is the retrospective design of the analysis. In the recommendation of the cooperative treatment trials, assessment of all tumour markers was not mandatory at recurrence of disease. In 51% of recurrences after complete treatment, any data from recurrence were missing due to incomplete staging because of the very poor prognosis of the seriously ill patients. Only in a few patients all tumour markers were available from recurrence (± 1 week). Patients with data available more frequently had localised disease and demonstrated a longer survival after disease recurrence. Therefore, we speculate that patients with a supposedly better prognosis at recurrence (i.e. localised disease) were more thoroughly tested than children with a supposed worse outcome (i.e. metastatic disease) which may result in a selection bias in favour of the better prognosis group. But the latter group might be clinically more relevant since treatment is more often successful in these patients (Fig. 1).

Nevertheless, the results allow the conclusion that relapse or progression in neuroblastoma cannot be detected or excluded reliably by monitoring tumour markers alone. This might be due to early detection of some recurrences when the patient still has a low tumour burden. Follow-up of neuroblastoma patients must include clinical assessment and imaging studies (ultrasound, CT, MRI and MIBG scintigraphy) as well as monitoring tumour markers. The question still remains as to whether early treatment of recurrent neuroblastoma might improve the poor prognosis of these patients.

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