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ORIGINAL REPORT

Excellent Outcome With Reduced Treatment for Infants With Disseminated Neuroblastoma Without *MYCN* Gene Amplification

Bruno De Bernardi, Mary Gerrard, Luca Boni, Hervé Rubie, Adela Cañete, Andrea Di Cataldo, Victoria Castel, Ana Forjaz de Lacerda, Ruth Ladenstein, Ellen Ruud, Benédicte Brichard, Jerome Couturier, Caroline Ellershaw, Caroline Munzer, Paolo Bruzzi, Jean Michon, and Andrew D.J. Pearson

From the Istituto Giannina Gaslini, and Istituto Nazionale Ricerca sul Cancro, Genova, Istituto Toscano Tumori, Firenze, and Università di Catania, Catania, Italy; Hôpital des Enfants, Toulouse, and Institut Curie, Paris, France; Hospital La Fe, Valencia, Spain; Instituto Português de Oncologia, Lisboa, Portugal; Rikshospitalet, Oslo, Norway; St Anna Kinderspital, Vienna, Austria; Saint Luc Cliniques Universitaires, Brussels, Belgium; Children's Cancer and Leukaemia Group Data Centre, University of Leicester, Sheffield Children's Hospital, and Institute of Cancer Research/Royal Marsden Hospital Sutton, United Kingdom.

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Corresponding author: Bruno De Bernardi, MD, Department of Hematology-Oncology, Giannina Gaslini Children Hospital, Largo Gerolamo Gaslini 5, 16148 Genova, Italy; e-mail: brunodebernardi@ospedale-gaslini.ge.it.

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ABSTRACT

Purpose
On the assumption that most infants with disseminated neuroblastoma without *MYCN* amplification (MYCNA) have a favorable prognosis, two concomitant prospective trials were started in which chemotherapy was limited to patients presenting life- or organ-threatening symptoms or overt metastases to skeleton, lung, or CNS. Surgery was to be performed only in the absence of surgical risk factors.

Patients and Methods
One hundred seventy infants with disseminated neuroblastoma without MYCNA, diagnosed between June 1999 and June 2004 in nine European countries were eligible for either of the two studies. Trial 99.2 included all stage 4S infants and those with stage 4 with a primary tumor infiltrating across the midline or positive skeletal scintigraphy who were to be observed in absence of symptoms. Trial 99.3 included infants with overt metastases to the skeleton, lung, and CNS to be treated with a minimum of four chemotherapy courses.

Results
The 125 infants treated on trial 99.2 had a 2-year overall survival (OS) of 97.6% with no difference between asymptomatic and symptomatic patients (97.7% *v* 97.3%), patients without or with unresectable primary tumors (96.8% *v* 100%), and patients without or with positive skeletal scintigraphy without radiologic abnormalities (97.2% *v* 100%). The 45 infants treated on trial 99.3 had a 2-year OS of 95.6%. No patients died of surgery- or chemotherapy-related complications.

Conclusion
Infants with disseminated disease without MYCNA have excellent survival with minimal or no treatment. Asymptomatic infants with an unresectable primary tumor or positive skeletal scintigraphy without radiologic abnormalities may undergo observation alone.

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INTRODUCTION

Disseminated neuroblastoma in the infant (0 to 11 months) has a more favorable prognosis than in older children.[1] One reason for this is the peculiar behavior of stage 4S disease,[2] which frequently undergoes spontaneous regression.[3] Stage 4S is defined by the International Neuroblastoma Staging System (INSS) as a "localized primary tumor (Stage 1, 2A or 2B) with disseminated disease limited to skin, liver and bone marrow in infants less than 1 year of age."[4] Furthermore, the INSS states that "bone marrow involvement in stage 4S should be minimal ie, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive bone marrow involvement would be considered stage 4. The MIBG scan should be negative in the marrow."[4]

In contrast to stage 4S, infants with stage 4 disease are believed to require chemotherapy to achieve cure.[3,5] Clinicians should clearly distinguish between these two patient subsets in order to only treat infants who may benefit from therapy, considering that tumors with *MYCN* amplification have a significantly worse outcome.[6]

However, there has been remarkable variability in the relative proportions of stage 4 and 4S patients reported in different series. In reports from the Pediatric Oncology Group[6,7] and Children's Cancer Group,[8,9] stage 4 patients outnumbered stage 4S (63% *v* 37%, and 65% *v* 35%, respectively). In contrast, two European series reported smaller

proportions of stage 4 patients compared with stage 4S: 31% *v* 69% in Italy[3] and 32% *v* 68% in Germany.[10] The different proportions of stage 4 and 4S disease may be due to inclusion of patients with scintigraphic positivity over the bone marrow or skeleton, or inclusion of stage 3 primary tumors, into either stage 4 or 4S.

In the late 1990s, French authors reported that infants classified as stage 4 due to a primary tumor infiltrating across the midline (INSS stage 3) or positive bone scintigraphy not associated with changes in the cortical bone documented on plain radiographs and/or computed tomography (CT), had a better outcome compared to other stage 4 infants (event-free survival [EFS] 90.0% *v* 27.2%).[11] They therefore hypothesized that a wait-and-see strategy could be applied to these patients. To test this hypothesis and in an effort to decrease the overall treatment burden of infants with disseminated neuroblastoma with favorable biologic features, in 1999 the European Neuroblastoma Group of the International Society of Pediatric Oncology (SIOPEN) activated two prospective uncontrolled trials—99.2 and 99.3. This article reports the results of these two trials.

PATIENTS AND METHODS

Patient Population and Eligibility

Infants with previously untreated disseminated neuroblastoma without amplification of *MYCN* gene, diagnosed between June 1999 and June 2004, were eligible for either 99.2 or 99.3 trials. Trial 99.2 comprised all infants with INSS stage 4S and infants classified as stage 4 disease only because of a primary tumor infiltrating across the midline and/or uptake in ^{123}I-metaiodobenzylguanidine (MIBG), or technetium^{99m} MDP (technetium) scintigraphy in the skeleton, but no detectable changes on plain radiographs and/or CT. Trial 99.3 included infants with tumor dissemination to the lung (intended as parenchymal lesions or pleural effusion), CNS, or skeleton, the latter defined by abnormal x-ray and/or CT. The trials were approved by the review boards of the participating institutions. Written informed consent was obtained from the patients' parents or legal guardians. Data were electronically centralized in the study database located at the 3ES Company, Paris, France.

Diagnosis

The diagnosis of neuroblastoma was mostly based on the examination of tumor specimens using the Shimada system[12] and the International Neuroblastoma Pathology Classification (INPC).[13] Unequivocal infiltration of the bone marrow by tumor cells was accepted as being diagnostic, provided that the mandatory biologic studies had been performed.

Pre-Treatment Investigation and Metastatic Work-Up

Patients' symptoms at presentation were graded according to Hsu et al[14] (Appendix Table A1, online only) and were scored 0 (absent), 1 (mild), or 2 (severe). Low symptom scores were 0 for neonates and up to 1 for older infants. High symptom scores were 1 or higher for neonates and 2 or higher for older infants. Imaging studies included ultrasonography plus CT and/or magnetic resonance imaging, MIBG, or technetium scintigraphy if MIBG was negative or not assessable. Any bony areas positive by either scintigraphy were to be evaluated by standard x-ray or CT when the skull was involved. Bone metastases were defined as changes in the cortical bone documented on plain radiographs and/or CT. Bone marrow was to be evaluated by a minimum of two aspirates. *MYCN* gene status in tumor cells was determined by fluorescence in situ hybridization (FISH) and centrally reviewed by the European Neuroblastoma Quality Assurance Group.[15] *MYCN* amplification was defined as more than four-fold increase of the *MYCN* signal number, as compared with the reference probe located on chromosome 2.[15] The assay of DNA index in tumor cells was strongly recommended.

Treatment

Surgery. To avoid the occurrence of severe surgery-related risks, if with reference to the previously described surgically defined–risk factors (SRFs)[16] the tumor was deemed unresectable, the surgeons were requested to limit the operation to a biopsy. In trial 99.2, the decision to resect the primary was left to the responsible physician, based on the lack of evidence supporting the beneficial effect of resections in these patients.[17] In trial 99.3, the primary was to be resected after chemotherapy, when feasible. Tumor resection was defined as being complete if there was no evidence of tumor on postoperative imaging. Resection was defined as incomplete if tumor was resected with macroscopic residue.

Chemotherapy: Trial 99.2. It was recommended that patients with low symptom scores not receive chemotherapy. Patients with high symptom scores were to receive two to four 3-day courses of carboplatin (6.6 mg/Kg/d) and etoposide (5 mg/Kg/d; CE). In case of persistent symptoms or progressive disease, up to four 5-day courses of cyclophosphamide (10 mg/Kg, days 1 to 5), doxorubicin (1 mg/Kg, days 4 and 5), and vincristine (0.05 mg/Kg, days 1 and 5; CAdO) were administered. Dosages were reduced by one third for neonates and infants weighing less than 5 Kg.

Chemotherapy: Trial 99.3. Treatment included two to four courses of CE as described above. Patients who did not respond to CE received 2 to 4 courses of CAdO. Patients who still failed to respond were treated individually.

Tumor responses were evaluated according to the International Neuroblastoma Response Criteria (INRC).[4] Complications were classified according to the National Cancer Institute Common Toxicity Criteria.[18]

Statistical Analyses

The aim of the studies was to demonstrate that the 2-year overall survival (OS) was greater than 85% for trial 99.2, and greater than 70% for trial 99.3. The median follow-up time was calculated on the entire cohort of patients according to the reverse Kaplan-Meier method; this method allows inclusion of all patients in the calculation.[19] The results of both trials were monitored at 6-month intervals to detect any possible excess in mortality and, in case, stop patient accrual. The hypotheses were tested by calculating the lower limit of the 95% two-sided exact CI of the 2-year overall survival (OS). OS was defined as the time between diagnosis and death, regardless of the cause. Disease progression, relapse, and death for any reason were considered events in event-free survival (EFS) analyses. OS and EFS were estimated according to the Kaplan-Meier product-limit method. Comparison of survival curves for the various subgroups was performed by log-rank test. Differences in patient distribution by characteristics at diagnosis between 99.2 and 99.3 trial subjects were assessed by the χ^2 test. All reported *P* values were two sided.

RESULTS

Between June 1999 and June 2004, a total of 181 infants with disseminated neuroblastoma without amplification of *MYCN* gene were enrolled by nine European countries (Austria, Belgium, France, Italy, Norway, Portugal, Spain, Switzerland, and United Kingdom). Of these 181 infants, 11 were excluded (of whom two died) for either incomplete skeletal studies (n = 5, including three who were too unwell to undergo any diagnostic procedures), or wrong trial allocation (n = 6), thus leaving 170 assessable infants, of whom 125 were enrolled in trial 99.2 and 45 in trial 99.3.

The main clinical and biologic features of the two patient subsets are listed in Table 1. There were similar numbers of males and females. Patients in trial 99.2 were significantly younger (median age, 3 *v* 7 months). The most common primary tumor site in both trials was the adrenal gland. An unresectable primary tumor was reported in 24% of trial 99.2 and in 56% of trial 99.3 patients. The most common metastatic sites were the liver in trial 99.2 and the bone in trial 99.3. An uptake in MIBG/technetium scintigraphy over the skeleton without radiologic changes was documented in 17 (13.6%) of trial 99.2 and in 10 (22.2%) of trial 99.3 patients. In the 17 trial 99.2 patients the

Table 1. Patients Characteristics at Diagnosis

Characteristic	Patients				
	99.2 Trial		99.3 Trial		
	No.	%	No.	%	*P*
Total	125	100.0	45	100.0	—
Sex					
Male	66	52.8	21	46.7	.480
Female	59	47.2	24	53.3	
Age, months					
0-1	43	34.4	4	8.9	< .001
2-5	56	44.8	15	33.3	
6-11	26	20.8	26	57.8	
Median	3		7		
Range	0-11		0-11		
Diagnosis					
Tumor biopsy histologic examination	117	93.6	41	91.1	
Presence of tumor cells in the bone marrow	8	6.4	4	8.9	
Primary site					
Adrenal	83	66.4	26	57.8	.209
Abdominal	19	15.2	8	17.8	
Thorax	13	10.4	4	8.9	
Neck/pelvis	2	1.6	4	8.8	
Multifocal	5	4.0	3	6.7	
Not detected	3	2.4	0	0	
Unresectable primary tumor					
Yes	30	24.0	25	55.6	
No	95	76.0	20	44.4	< .001
Bone abnormal by scan (normal x-ray/CT)	17	13.6	10	22.2	—
Metastases					
Liver	97	79.7	23	51.1	.001
Bone marrow	41	32.8	28	62.2	.001
Bone abnormal by x-ray/CT	0	0	33	73.3	—
Skin	22	17.6	10	22.2	.511
Lung	0	0	12	26.7	NA
CNS	0	0	5	11.1	NA
Shimada histology (88 NE)					
Favorable	39	58.2	7	46.7	.416
Unfavorable	28	41.8	8	53.3	
DNA index (83 NT)					
Aneuploid	41	82.0	9	52.9	.017
Diploid/tetraploid	9	18.0	8	47.1	

Abbreviations: CT, computed tomography; NA, not applicable; NE, not assessable; NT, not tested.

positive scintigraphy was obtained by MIBG in 15 patients and by technetium in two. While none of these 17 patients in trial 99.2 had changes on plain radiographs or CT, 33 of 45 trial 99.3 patients had detectable radiological bone changes. Metastatic involvement of the lung (n = 12 including three parenchymal lesions and nine pleural effusions) and CNS (n = 5) was documented in trial 99.3. Diploid or tetraploid DNA index was detected less frequently in 99.2 than in trial 99.3 patients (18.0% *v* 47.1%).

Table 2. Resection of Primary Tumor

Type of Resection	Trial 99.2 Patients (n = 125)				Trial 99.3 Patients (n = 45)			
	No.	%	At Diagnosis	Delayed	No.	%	At Diagnosis	Delayed
Complete	52	41.6	34	18	25	55.7	1	24
Incomplete	10	8.0	4	6	5	9.0	1	4
Any	62	49.6	38	24	30	66.7	2	28
None	63	50.4	87	101	15	33.0	43	17

Table 3. Clinical Course and Outcome of Four Cohorts of Patients in Trial 99.2

Cohort: INSS Primary Tumor Stage	Cohort: Uptake in MIBG/ Technetium Scintigraphy	No. of Patients	No. of Patients Who Underwent First-Line Chemotherapy	No. of Courses: Median	No. of Courses: Range	Clinical Course	Outcome	Deaths
1 or 2 (INSS stage 4S)	No	84	41	0	0-6	13 patients underwent tumor progression	−1 died rapidly; −6 received SD: 3 died, 3 alive; −6 received HD: 1 died, 5 alive	5
1 or 2	Yes	11	7	1	0-6	2 patients underwent tumor progression	−1 received SD: alive; −1 received HD: alive	0
3	No	24	16	2	0-6	1 patient underwent tumor progression	Received SD: alive	0
3	Yes	6	4	2	0-4	No event	−6 alive	0

NOTE. Of 17 patients with positive scintigraphy, eight underwent scintigraphic evaluation that resulted negative in 5 and positive in 3.
Abbreviation: INSS, International Neuroblastoma Staging System; MIBG, ^{123}I-metaiodobenzylguanidine; technetium, technetium^{99m} MDP; SD, standard-dose chemotherapy; HD, high-dose chemotherapy with hemopoietic stem cell rescue.

Surgery and Clinical Course

Surgery: Trial 99.2. Complete primary tumor resection was carried out in 52 (41.6%) of 125 patients. In addition, 10 other patients underwent incomplete resection, giving an overall resection rate of 49.6% (Table 2).

Surgery: Trial 99.3. Complete resection of the primary tumor was achieved in 25 (55.6%) of 45 patients. Five other patients underwent incomplete tumor resection, giving an overall resection rate of 66.7% (Table 2).

Surgical Complications

There were no surgery-related deaths. Of 92 tumor resections, nine (9.9%) were followed by grade 3 or 4 transient complications, including perioperative hemorrhage (n = 3), intestinal obstruction

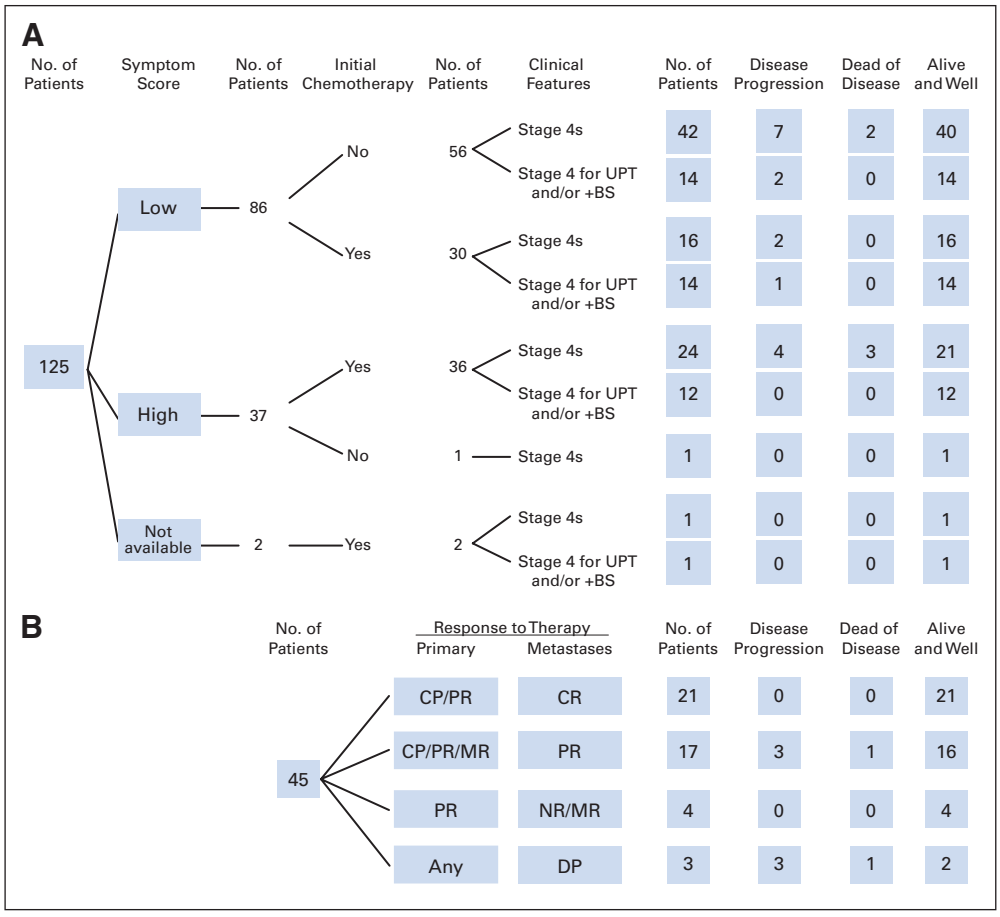

Fig 1. Clinical course and outcome of (A) 99.2 trial and (B) 99.3 trial patients in relation to response to therapy. UPT, unresectable primary tumor; +BS, positive bone scan; CR, complete response; PR, partial response; MR, minor response; NR, no response; DP, disease progression.

(n = 2), renal insufficiency (n = 2), sepsis (n = 1), and delayed wound healing (n = 1). In addition, two resections were followed by permanent Horner syndrome.

Clinical Course

Trial 99.2. Of 125 infants, 16 developed disease progression and five died. Details of clinical course according to the four cohorts, defined by metastatic spread and primary tumor INSS stage, are presented in Table 3.

Infants with low symptom scores. Fifty-six of 86 infants underwent observation only. There was disease progression in nine and two deaths (Fig 1A). After the investigators' decisions, the remaining 30 infants received chemotherapy (one to two courses in 24 patients; four to six courses in six patients). There was disease progression in three patients and no deaths (Fig 1A).

Infants with high symptom scores and infants not evaluated by symptom scores. Thirty-six of 37 patients received chemotherapy (one to two courses in 29 patients, three courses in one patient, and four courses in six patients) according to protocol (Fig 1A). There was disease progression in four patients and three deaths (Fig 1A). The only untreated patient fared well (Fig 1A).

The two patients who were not evaluated by symptom score were treated with two chemotherapy courses and did well (Fig 1A).

Trial 99.3. Six of 45 infants developed disease progression and two died. Patients received a median of six courses (range, two to eight courses) of chemotherapy.

Twenty-one infants achieved complete remission with chemotherapy alone (n = 6), or chemotherapy followed by surgery (n = 15), and are alive (Fig 1B).

Of 17 patients who achieved partial metastatic response, 13 received no further therapy (11 are alive without further therapy, two had disease progression, and one died). Four patients received additional chemotherapy (including two treated by high-dose chemotherapy with hematopoietic stem cell rescue) with one disease progression and no deaths (Fig 1B).

Four patients had minor or no metastatic response and are alive and well (Fig 1B). Three patients developed disease progression during initial chemotherapy, of whom two are alive and one died (Fig 1B).

Chemotherapy-related toxicities. Primary chemotherapy was administered to 112 infants for a total of 402 courses, of which 393 were assessable for toxicity. There were no chemotherapy-related deaths. Grade 3 to 4 nonhematologic toxicity included sepsis (n = 15), pulmonary infection (n = 9), diarrhea (n = 7), liver insufficiency (n = 3), renal toxicity (n = 2), seizure (n = 1), and tumor lysis syndrome (n = 1).

Analysis of Survival

Median follow-up for both trials was 52 months. The 2-year and 5-year OS for trial 99.2 were 97.6% (95% CI, 94.9 to 100) and 95.7% (95% CI, 92.0 to 99.4), respectively (Table 4). The 86 patients with low symptom scores (56 did not receive and 30 received first-line chemotherapy) in trial 99.2 had a 2-year OS of 97.7% (95% CI, 94.6 to 100), and similar outcomes were observed in patients who were either initially untreated or treated (96.4% *v* 100%; $P = .478$). OS was 90.4% (95% CI, 79.8 to 100) for the 37 patients presenting with high symptom scores. No fatalities were recorded in the 41 patients on trial 99.2 who did not have INSS stage 4S (Table 4). In trial 99.3, both 2-year and 5-year OS were 95.6% (95% CI, 89.5 to 100; Fig 2A). No differences in OS were seen between patients in trials 99.2 and 99.3.

The 2-year and 5-year EFS were 88.8 (95% CI, 83.3 to 94.3) and 87.8% (95% CI, 81.9 to 93.7) for trial 99.2, while they were 86.7% (95% CI, 76.7 to 96.7) for both 2-year and 5-year EFS in trial 99.3 (Fig 2B). The 2-year EFS of trial 99.2 was comparable in patients presenting with low and high symptom scores (87.2% *v* 87.9%). It was also

Table 4. Two- and 5-Year OS and EFS of 99.2 and 99.3 Trial Patients

		2 Year				5 Year			
Trial	Patients	OS	95% CI	EFS	95% CI	OS	95% CI	EFS	95% CI
99.2	125	97.6	94.9 to 100	88.8	83.3 to 94.3	95.7	92.0 to 99.4	87.8	81.9 to 93.7
Low symptom scores*	86	97.7	94.6 to 100	87.2	80.1 to 94.3	97.7	94.6 to 100	87.2	80.1 to 94.3
Untreated	56	96.4	91.5 to 100	85.7	76.5 to 94.9	96.4	91.5 to 100	85.7	76.5 to 94.9
Treated	30	100	—	90.0	79.2 to 100	100	—	90.0	79.2 to 100
High symptom score	37	97.3	92.1 to 100	91.9	76.0 to 100	90.4	79.8 to 100	87.9	76.5 to 99.3
Unresectable primary									
Yes	30	100	—	93.3	84.4 to 100	100	—	93.3	84.4 to 100
No	95	96.8	93.3 to 100	87.4	80.7 to 94.1	94.4	89.6 to 99.2	86.1	79.1 to 93.1
Bone involvement									
Absent	108	97.2	94.1 to 100	88.0	81.9 to 94.1	95.0	90.7 to 99.3	86.8	80.3 to 93.3
By positive scan only	17	100	—	94.1	82.9 to 100	100	—	94.1	82.9 to 100
99.3	45	95.6	89.5 to 100	86.7	76.7 to 96.7	95.6	89.5 to 100	86.7	76.7 to 96.7
Unresectable primary									
Yes	25	96.0	88.3 to 100	84.0	69.6 to 98.4	96.0	88.3 to 100	84.0	69.6 to 98.4
No	20	95.0	85.5 to 100	90.0	76.8 to 100	95.0	85.5 to 100	90.0	76.8 to 100
Bone involvement									
By positive scan only	10	90.0	71.4 to 100	90.0	71.4 to 100	90.0	71.4 to 100	90.0	71.4 to 100
By x-Ray/CT	33	97.0	91.2 to 100	84.9	72.7 to 97.1	97.0	91.2 to 100	84.9	72.7 to 97.1

Abbreviations: OS, overall survival; EFS, event-free survival; CT, computed tomography.
*Symptom scores unknown in two patients.

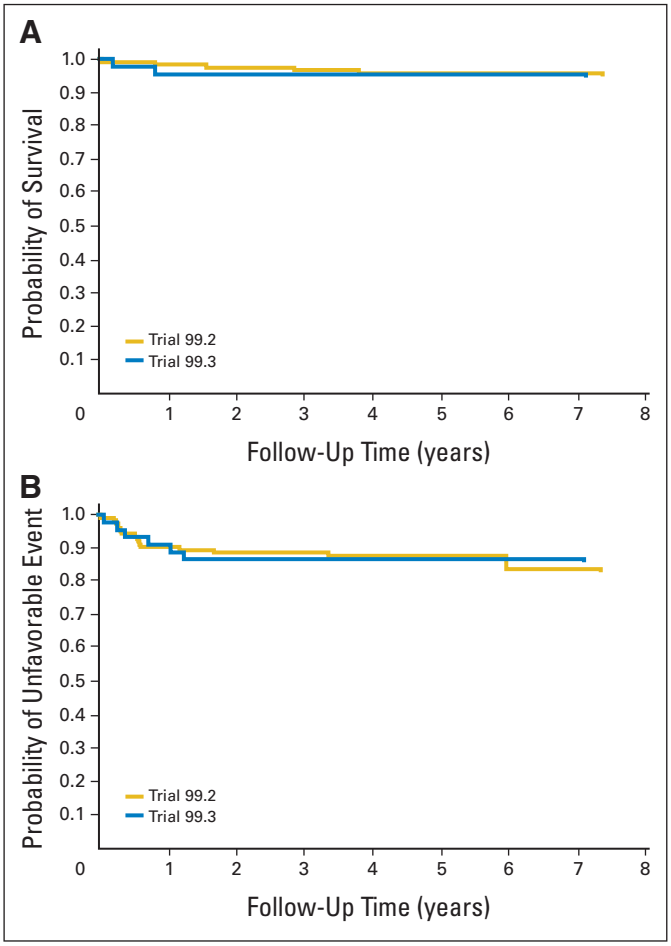

Fig 2. (A) Overall survival and (B) event-free survival of 99.2 and 99.3 trial patients.

comparable in infants with low symptom scores, both initially untreated (n = 56) and treated (n = 30; 85.7% *v* 90.0%), in infants with or without an unresectable primary tumor (93.3% *v* 86.1%), in infants with or without positive MIBG/technetium scintigraphy (94.1% *v* 86.8%; Table 4), and in infants with favorable (n = 39) or unfavorable (n = 28) Shimada histology (87.2% *v* 92.9%). The only difference detected regarded DNA index, with better EFS for infants having aneuploid (n = 41) versus diploid/tetraploid (n = 9) index (95.1% *v* 58.3%; $P = .005$).

DISCUSSION

The main aim of these two studies was to assess whether a substantial reduction in the overall treatment burden of infants with disseminated neuroblastoma without *MYCN* gene amplification would compromise the good outcome of these patients, while avoiding the toxicity, mortality, and long-term sequelae secondary to more aggressive therapeutic approaches. To reach this goal, some changes to the commonly accepted therapeutic guidelines applied to these infants were made.

First, to minimize surgery-related risks, the SRFs previously identified by our own group[16] were considered before any operations. As a consequence of this approach, no surgery-related deaths were recorded in the 170 patients enrolled in the two trials, and only 9 severe complications were observed, all of which were transient.

Second, infants who were classified as stage 4 because of an INSS stage 3 primary or uptake in MIBG/technetium scintigraphy with no detectable changes on plain radiographs and/or CT were assigned to follow a wait-and-see strategy. In addition, chemotherapy that was necessary for infants presenting with tumor-related symptoms was administered only as long as symptoms persisted. Finally, infants with overt metastatic involvement of the skeleton, lung, and CNS underwent standard-dose chemotherapy regimens, and even lower doses were adopted for very young or low-weight infants. This cautious attitude was rewarded by the absence of any chemotherapy-related deaths.

Based on our results, infants with metastases involving the lung, CNS, and skeleton confirmed by x-ray/CT should require therapy. The remainder of infants with disseminated disease could be observed and only treated if they have life-threatening symptoms. In doing so, the majority of enrolled infants (ie, 125 of 170) were assigned to the trial 99.2, and could avoid initial chemotherapy if asymptomatic. However, only 56 of 86 asymptomatic infants followed the protocol guidelines and were observed with seven progressions and two deaths, while the physicians responsible for the remaining 30 infants believed that chemotherapy was required, resulting in three disease progressions but no deaths. This underlines the fact that a wait-and-see strategy for these children may not yet be acceptable for a number of pediatric oncologists. It is important that none of the 41 infants presenting with an INSS stage 3 primary or positive scintigraphy associated with radiologic changes died, regardless of initial chemotherapy. The 100% OS for these 41 infants compares favorably with previous reports treating these patients as stage 4 disease with multiple courses of chemotherapy.[3,6-11] The 95.7% OS for all patients on 99.2 is equivalent or better than previously published experiences,[3,6-11] where more chemotherapy was administered and in our view justifies therapeutic protocols made of short- and standard-dose chemotherapy regimens.

By limiting patient enrollment in trial 99.3 to infants with overt metastatic involvement of the skeleton, lung, or CNS, one might expect high progression and death rates. On the contrary, only six of these 45 infants developed disease progression and only two eventually died, resulting in 2-year EFS and OS rates comparable to trial 99.2. Only 21 of these 45 infants achieved complete metastatic response with protocol chemotherapy. Thirteen of 17 with a metastatic partial response received no further therapy and 11 are alive, thus confirming that stage 4 disease in infants without amplification of *MYCN* is less aggressive than at older ages.[20] However, with regards to both stage 4 and 4S infants with *MYCN* gene amplification, we recently reported[21] the same dismal outcome described by others,[6,11] despite aggressive treatment.

The excellent survival rates achieved in our studies have to be tempered by the fact that patient enrollment was only possible after *MYCN* gene status had been properly evaluated. On account of this requirement, some patients with unfavorable prognosis were excluded from enrollment in either trial since they could not undergo biopsy to obtain tumor material because of their poor presenting conditions. This limitation may possibly be overcome in the near future through technologies that will allow us to measure *MYCN* gene products in the blood.[22]

In conclusion, our studies confirm that disseminated neuroblastoma in infants without *MYCN* gene amplification has a favorable outcome in most cases. In addition, they suggest that an observational strategy is possible regardless of primary tumor resectability and uptake in MIBG/technetium scintigraphy, provided that this is not associated to radiologic changes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Bruno De Bernardi, Mary Gerrard, Luca Boni, Adela Cañete, Jerome Couturier, Paolo Bruzzi, Andrew D.J. Pearson

Provision of study materials or patients: Mary Gerrard, Hervé Rubie, Adela Cañete, Andrea Di Cataldo, Victoria Castel, Ana Forjaz de Lacerda, Ruth Ladenstein, Ellen Ruud, Bénédicte Brichard, Andrew D.J. Pearson

Collection and assembly of data: Mary Gerrard, Luca Boni, Hervé Rubie, Adela Cañete, Andrea Di Cataldo, Victoria Castel, Ellen Ruud, Jerome Couturier, Caroline Ellershaw, Caroline Munzer, Jean Michon

Data analysis and interpretation: Bruno De Bernardi, Luca Boni, Hervé Rubie, Adela Cañete, Andrea Di Cataldo, Ruth Ladenstein, Jerome Couturier, Paolo Bruzzi, Jean Michon, Andrew D.J. Pearson

Manuscript writing: Bruno De Bernardi, Mary Gerrard, Luca Boni, Victoria Castel, Jerome Couturier, Paolo Bruzzi, Jean Michon, Andrew D.J. Pearson

Final approval of manuscript: Bruno De Bernardi, Mary Gerrard, Luca Boni, Hervé Rubie, Adela Cañete, Andrea Di Cataldo, Victoria Castel, Ana Forjaz de Lacerda, Ruth Ladenstein, Ellen Ruud, Bénédicte Brichard, Jerome Couturier, Caroline Ellershaw, Caroline Munzer, Paolo Bruzzi, Jean Michon, Andrew D.J. Pearson

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