Chronic Neuroblastoma

Indolent Stage 4 Disease in Children

Brian H. Kushner, M.D.
Kim Kramer, M.D.
Nai-Kong V. Cheung, M.D., Ph.D.

Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York.

Supported in part by National Cancer Institute Grants CA61017 and CA72868, the Robert Steel Foundation, the Katie’s Find A Cure Fund, and the Justin Zahn Fund.

Address for reprints: Brian H. Kushner, M.D., Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; Fax: 212-717-3239; E-mail: kushnerb@mskcc.org

BACKGROUND. An indolent course is associated with neuroblastoma (NB) in adolescents and adults. In the current study, the authors analyzed this phenomenon in a large series of children with metastatic NB.

METHODS. The authors studied 38 patients who were diagnosed with NB in the first decade of life and had metastatic disease 5 years or more from diagnosis.

RESULTS. The median age at diagnosis was 3 years 10 months. MYCN was amplified in 2 of 28 patients tested. Of 30 patients with classic Stage 4 NB, 9 had a late first recurrence of disease (4.3–13 years from diagnosis). Of eight patients who had atypical cases at diagnosis (one isolated mandibular lesion, two Stage 4-N, five non-Stage 4), six had a late first distant recurrence of disease (4 years 11 months–38 years 8 months). Nineteen patients were off therapy continuously for 3 years or more before disease recurred a first or second time. Myeloablative therapy was used to consolidate a first or second response in 27 patients. High-dose conventional therapy helped to achieve a second remission of disease in 9 of 20 patients assessable for response of first recurrence but achieved no major responses of second or third relapse in 10 of 11 patients. The combination of anti-GD2 immunotherapy and/or cis-retinoic acid, targeted radiotherapy, and multiple cycles of chemotherapy with modest toxicity helped prolong survival. Twelve patients survive at 5 years 6 months+ to 19 years 4 months+ from diagnosis (median, 6 years 10 months+), including four with complete remission of disease; 10 received anti-GD2 immunotherapy after recurrence. The other 26 patients died of disease (n = 22) or toxicity (n = 4) at 5 years–41 years 5 months from diagnosis (median, 6 years 5 months).

CONCLUSIONS. The concept of indolent or smoldering NB should not be limited to adolescents/adults. The expanding repertoire of anti-NB treatments, including biologic therapies and chemotherapy regimens of modest toxicity, can convert childhood NB into a chronic disease with prolonged survival after recurrence.

Cancer 2002;95:1366–75. © 2001 American Cancer Society.
DOI 10.1002/cncr.10800

KEYWORDS: neuroblastoma, chronic disease, indolent disease, biologic therapy, chemotherapy.

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood and greater than 95% of cases are detected by 10 years of age.1 NB exhibits age-related natural histories: in infants, both localized and metastatic forms are highly curable2; in children, localized forms are highly curable with conservative management3 but metastases at presentation herald a progressive lethal course4; and in adolescents and adults, the prognosis with both localized and metastatic forms is poor although the clinical course may be protract- ed.3–7 MYCN amplification is detected in one third of the cases of advanced-stage NB1,2 but is extremely rare in adolescents/adults.6,7
| Patient no. | Gender | Age at diagnosis | Ferritin (ng/mL) | LDH/MYCN-amplified | Initial presentation sites: treatment | First recurrence time from diagnosis: sites: treatment | Second and subsequent recurrence(s) time from diagnosis: sites: treatment | Outcome (time from diagnosis) |
|------------|--------|-----------------|-----------------|-------------------|--------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------|
| 1          | Female | 1yr 8mos        | 58/.../...      |                    | R Adr, B, L: neck; S, CCG(× 5), RT, BMT | 3yrs7mos: Skull/orbit: N5(× 1), P/E(× 2) Cy(E(× 2), S, RT | 4yrs10mos: BM, B, L neck, liver, lungs: RT | DoD (5yrs2mos) |
| 2          | Male   | 2yrs 8mos       | 148/843/no      | no                 | R, BM, neck: CCG(× 5 + 3), CRA       | 2yrs11mos: Orbit, neck: CCG(× 5), SCT, CRA | 4yrs4mos: Orbit: To(× 1), RT, oral E(× 5), Cy*/To/V(× 3) | DoD (6yrs2mos) |
| 3          | Male   | 2yrs 9mos       | 80/266/yes      | yes               | R Adr, BM: CCG(× 5), S, RT, BMT       | 3yrs10mos: Ankle: RT                            | 4yrs3mos: BM, B: 3F8, RT                      | DoD (5yrs) |
| 4          | Male   | 2yrs 11mos      | .../.../no      |                   | R, B, BM: POG(× 6), S, BMT            | 3yrs6mos: RP, B, BM: POG(× 6), S, RT, 3F8, Cy* CRA | 4yrs2mos: RP, B, BM: Phase agents | DoD (5yrs2mos) |
| 5          | Male   | 2yrs 11mos      | 52/383/no       | yes               | R Adr, BM: CCG(× 5), S, RT, BMT       | 1yrs1mos: BM: N7(× 3), Cy*(× 1), BMT            | 5yrs4mos: RP, B, BM: To/CRA (× 11mos)        | AvnD (8yrs1mos+) |
| 6          | Female | 3yrs            | 339/.../no      |                   | R Adr, B, BM: CCG(× 5 + 3), S         | 2yrs5mos: BM: N7(× 4), 3F8, RT                  | 5yrs7mos: BM: oral E/CRA(× 18mos)            | DoD (6yrs) |
| 7          | Male   | 3yrs 3mos       | 558/668/...     |                   | R, B, BM: COD = M(× 4), S, RT, alloBMT | 1yrs5mos: RP: Cy × Dox(× 4), RT, 3F8            | 2yrs8mos: RP, B, RT, COD(× 3)                | DoD (5yrs7mos) |
| 8          | Male   | 3yrs 4mos       | .../.../.../...  |                   | R Adr, BM: CCG(× 5), S, RT, BMT       | 1yrs7mos: BM: I/E(× 1), P/E(× 2), BMT          | 2yrs8mos: BM, B: RT, Cy*(× 2), 3F8            | DoD (5yrs1mo) |
| 9          | Female | 3yrs 6mos       | 187/637/no      |                   | Pelvis, B, BM: CCG(× 5), S, RT, BMT   | 2yrs11mos: RP: ICE(× 3), 3F8                    | 4yrs4mos: RP, B: MoAb, To(× 9)               | DoD (5yrs10mos) |
| 10         | Male   | 3yrs 8mos       | .../.../.../...  |                   | R Adr, BM: S, P × E(× 8)              | 2yrs1mos: Th-RP, B, BM: RT, ICE(× 9)           | 5yrs11mos: BM: N6(× 7), 3F8                   | DoD (5yrs7mos) |
| 11         | Male   | 3yrs 9mos       | 94/257/no       |                   | Th, B, BM: CCG(× 5), S, RT, SCT       | 2yrs1mos: Th, B, BM: N6(× 7), CRA             | 3yrs: Th, B, BM: Cy/To(× 2), 3F8, 3yrs8mos: BM, L sc: RT, Cy/To(× 8), vaccine, 3yrs9mos: BM, L, Cy/P/Dox(× 3) | DoD (5yrs6mos) |
| 12         | Male   | 3yrs 9mos       | 252/.../.../...  |                   | R Adr, BM, B: S, CAV/P(× 1yr), 3F8    | 3yrsmos: RP, B, BM: I/E(× 6), N5(× 2), RT     | 4yrs11mos: Liver, B: CRA                      | DoD (6yrs7mos) |
| 13         | Male   | 3yrs 10mos      | 138/1196/no     |                   | L Adr, BM, B: S, To(× 2), POG(× 6), RT, BMT | 1yrs5mos: BM, B, L neck: I/E(× 6), To(× 21mos), vaccine | 4yrs4mos: RP, B, BM: oral E(× 2), To(× 5), phase agents | DoD (6yrs4mos) |
TABLE 1 (continued)

| Patient no. | Gender | Age at diagnosis | Ferritin (ng/mL) | LDH/MYC/N-amplified | Initial presentation sites: treatment | First recurrence time from diagnosis: sites: treatment | Second and subsequent recurrence(s) time from diagnosis: sites: treatment | Outcome (time from diagnosis) |
|-------------|--------|------------------|------------------|----------------------|---------------------------------------|--------------------------------------------------------|--------------------------------------------------------|-------------------------------|
| 14          | Male   | 4yrs 3 mos       | 152/1247/...     | L Adr, B, PO/G(×11), S, RT, SCT | 3yrs3mos: B: Cy/(To(×14) | 4yrs1mos: B: oral To(×6), RT | DoD (7yrs9mos) |                               |
| 15          | Male   | 4yrs 1 mo        | 451/708/no       | L Adr, B, CC/G(×5 + 3), S | 2yrs3mos: RP: S, N7/(×7), RT, 13I-3F8, 3F8 | 6yrs1mos: B: Cy*/To(×3), P*/To(×1), 3F8 | DoD (5yrs1mos) |                               |
| 16          | Female | 4yrs 1 mo        | 451/708/no       | L Adr, B, CC/G(×5 + 3), S | 2yrs3mos: RP: S, N7/(×7), RT, 13I-3F8, 3F8 | 6yrs1mos: B: Cy*/To(×3), P*/To(×1), 3F8 | DoD (5yrs1mos) |                               |
| 17          | Male   | 4yrs 6 mos       | 451/708/no       | L Adr, B, PO/G(×11), S, RT, SCT | 3yrs3mos: B: Cy/(To(×14) | 5yrs1mos: B: oral To(×6), RT | DoD (7yrs9mos) |                               |
| 18          | Male   | 5yrs 3 mos       | 451/708/no       | L Adr, B, CC/G(×5 + 3), S | 2yrs3mos: RP: S, N7/(×7), RT, 13I-3F8, 3F8 | 6yrs1mos: B: Cy*/To(×3), P*/To(×1), 3F8 | DoD (5yrs1mos) |                               |
| 19          | Female | 4yrs 11 mos      | 451/708/no       | L Adr, B, PO/G(×11), S, RT, SCT | 3yrs3mos: B: Cy/(To(×14) | 5yrs1mos: B: oral To(×6), RT | DoD (7yrs9mos) |                               |
| 20          | Male   | 7yrs 2 mos       | 451/708/no       | L Adr, B, Th: MADDOC(×14), S | 3yrs3mos: L: Adr, B, N6/(×7), S, RT, 13I-3F8, 3F8 | 7yrs5mos: R: B, BM, neck: CRA | AwD (7yrs10mos+) |                               |
| 21          | Female | 6yrs 11 mos      | 451/708/no       | L Adr, B, PO/G(×11), S, RT, SCT | 3yrs3mos: B: Cy/(To(×14) | 5yrs1mos: B: oral To(×6), RT | DoD (7yrs9mos) |                               |

Abbreviations: 3F8: anti-G D2 monoclonal antibody; Adr: adrenal gland; AwD: alive with disease; B: cortical bone; BM: bone marrow transplantation after high-dose alkylator ± P; CAV: Cy/Dox/V; CC/G: P/E/Dox/Cy(× 5) ± P/Dox/E(× 3); COX: Cy/Dox/V; cytotoxic agents; Cy: cyclophosphamide; DoD: died of disease; Dox: doxorubicin; E: etoposide; I: ifosfamide; ICE: I/P/E; LDH: lactate dehydrogenase (U/L); M: melphalan; MADDCC: mustard/Dox/P/Cy/V/dacarbazine; MIBG: metaiodobenzylguanidine; MoAb: anti-G D2 monoclonal antibody 14.18; N: four to six cycles of escalating doses of Cy(60–140 mg/kg) plus Dox(30 mg/m²)/V; cell cycle-specific agents; N6: Cy*/Dox(65 mg/m²)/V; N7/N7: Cy*/Dox(75 mg/m²)/V; alternating with P*/E: NB: neuroblastoma; P: carboplatin or cisplatin; POG: cycles of P*/E: CAV: I/E; R: retroperitoneum; RT: radiotherapy; S: surgical resection; sc: supravacular; SCT: peripheral blood stem cell transplantation after high-dose alkylator ± P; t-AML: treatment-related preleukemia; Tem: temozolomide; Th: thorax; To: topotecan; V: vincristine.

* Denotes high-dose chemotherapy: cyclophosphamide 140 mg/kg, i.e., ~4200 mg/m²; ifosfamide 10 g/m²; or cisplatin 200 mg/m².

Its absence has been cited as a possible contributory factor underlying the indolent behavior of NB in older patients. Other useful adverse prognostic markers include high serum levels of ferritin (> 150 ng/mL for children) and lactate dehydrogenase (LDH; > 1500 U/L). The latter is associated with short survival.

A protracted clinical course of metastatic NB in children has been the subject of case reports and is noted in a recent survey by the European Neuroblastoma Study Group. The European Neuroblastoma Study Group described the outcome, but not the treatments or the biologic markers, of patients who were diagnosed with NB between 1982 and 1990 and were alive at 5 years. We present an analysis of our experience with children who had metastatic NB 5 years or more from diagnosis. The expanding repertoire of anti-NB treatments, including biologic therapies and chemotherapy regimens with modest toxicity, can convert childhood NB into a chronic disease.

**MATERIALS AND METHODS**

This study covers 38 patients who were younger than 10 years old when diagnosed with NB, who had metastatic disease 5 years or more from diagnosis, and
TABLE 2
Patients with Classic Stage 4 Disease and Very Late Recurrence

| Patient no. | Gender | Age at diagnosis | Ferritin (ng/mL) | LDH/MYCN-amplified | Initial presentation Sites: treatment | First recurrence Time from diagnosis: sites: treatment | Second and subsequent recurrence(s) Time from diagnosis: sites: treatment | Outcome (time from diagnosis) |
|-------------|--------|------------------|------------------|--------------------|--------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------|
| 22          | Female | 2yrs 2mos        | 460/687/no       |                    | B, BM: CCG(× 5 + 3), S, RT, SCT     | 4yrs3mos: B, BM: S, RT, Cyt/To/V(× 3), Cyt*/To/V(× 1), 3F8/oral E | 5yrs5mos: L5, oral To(× 7), RT                | AwD (6yrs8mos+)             |
| 23          | Female | 2yrs 7mos        | 385/1834/no      |                    | Th, B, BM: CCG(× 4), S, RT, 131I-MIBG/BMT | 5yrs3mos: B, BM: N7(× 4), 131I-3F8, 3F8       | 6yrs3mos: Cyt*/CPT-11(× 1), 131I-MIBG          | DoD (8yrs1mo)               |
| 24          | Male   | 3yrs             | . . . . /no      |                    | B, BM: COD(× 25)                  | 6yrs10mos: Skull: COD(× 2), RT, 3F8             | 9yrs4mos: B, neck: S, P/E(× 3), RT, 3F8       | Toxic death/PD (10yrs5mo)    |
| 25          | Female | 3yrs 5mos        | . . . . /no      |                    | B, BM: POG(× 5), RT, SCT(× 2), CRA | 5yrs7mos: Skull: Cyt*/To/V(× 1), RT, oral To(× 1), 3F8 | 6yrs2mos: B, neck: Doc ∗ V(× 2), RT, CPT-11(× 2), P/oral E(× 2mos), 131I-MIBG | AwD (8yrs11mos+)             |
| 26          | Female | 3yrs 10mos       | . . . . /no      |                    | Th, B, BM: CCG(× 5 + 3), S, CRA     | 8yrs3mos: BP: N7(× 4), P/E(× 1), S, SCT, RT, 3F8/oral E, CRA | —                               | CR2 (10yrs6mos+) on CRA     |
| 27          | Male   | 4yrs 7mos        | 231/249/ . . .   |                    | L, Adr, B, BM: S, N5(× 6), P/E(× 6), RT, 131I-3F8/BMT | 13yrs: Pelvis, B, BM: Cyt*/P/E(× 1), Cyt*/Dox/V(× 2), Cyt*/To/V(× 2), phase agents | —                               | AwD (14yrs1mo+)             |
| 28          | Male   | 4yrs 10mos       | . . . . /1435/no |                    | L, Adr, B, BM: CCG(× 5), RT, BMT, CRA | 5yrs1mos: RP, B, BM, lymph nodes, liver: N7(× 7), RT, 131I-3F8, 3F8 | 6yrs6mos: liver: oral E                  | DoD (7yrs3mos)              |
| 29          | Female | 7yrs 3mos        | . . . . /no      |                    | L, Adr, B, BM: RT, COD(× 15), S, N4(× 5) | 7yrs2mos: Skull: S, RT, N4(× 4), 3F8 | —                               | CR2 (19yrs6mos+)           |
| 30          | Male   | 8yrs 11mos       | . . . . /no      |                    | RP, B, BM: CAV(× 6), P/E(× 6)       | 4yrs7mos*: RP, B, BM: N7(× 5), S, 3F8, SCT, 3F8/oral E | —                               | CR2 (8yrs9mos+) on 3F8/oral E |

See abbreviations and ** footnote in Table 1.

* Residual viable NB resected 5yrs2mos from diagnosis, NB in BM through 5yrs7mos.

who were followed in the Memorial Sloan-Kettering Cancer Center (MSKCC) Department of Pediatrics since 1987 (Tables 1–3). Recurrence of disease more than 4 years from diagnosis was defined as “very late.” Five patients received no (Patients 27, 33, 36, 38) or minimal therapy (Patient 15) before coming to MSKCC and one patient (Patient 12) was referred for consolidation of first remission. Other patients were referred to MSKCC for treatment of primary refractory disease (incomplete response to initial therapy; Patients 14, 17, 29); for treatment of newly identified and untreated first (Patients 5, 20, 21, 23, 28, 30), second (Patients 1, 3, 10, 31, 34), or third (Patient 35) recurrence; or for additional treatment of first (Patients 4, 6, 7, 9, 11, 16, 22, 25, 26), second (patients 8, 13, 18, 24, 32, 37), or third (patients 2, 19) recurrence. International criteria were used to establish the diagnosis and the stage.15 Stage 4 by virtue of distant lymph node metastases alone was labeled Stage 4-N. 16 Informed consent for treatment at MSKCC was obtained in accordance with hospital rules.

Disease status was assessed at MSKCC by computed tomography scan, 99mTc bone scan, 131I- or 123I-metaiodobenzylguanidine (MIBG) scan, and urine vanilmandelic acid (VMA) and homovanillic acid (HVA) measurements. Bone marrow (BM) was evaluated by histochemical examinations of two biopsy specimens (bilateral posterior iliac crests) and four aspirates (bilateral anterior and bilateral posterior iliac crests).
Disease status at MSKCC was categorized by the International Neuroblastoma Response Criteria: complete response (CR), no evidence of disease; very good partial response, primary mass reduced by 90–99%, no evidence of distant disease except for skeletal residua, catecholamines normal; partial response (PR), greater than 50% decrease in measurable disease and 1 or no positive BM site; mixed response, greater than 50% decrease of any lesion with less than 50% decrease in any other; no response, less than 50% decrease but less than 25% increase in any lesion; and progressive disease (PD), new lesion or greater than 25% increase in an existing lesion.

Chemotherapy regimens were classified as low-dose, moderate-dose, or high-dose.

### TABLE 3
Atypical Cases of Active Metastatic NB ≥ 5 Years from Diagnosis

| Patient no. | Gender | Age at diagnosis | Ferritin (ng/mL) | LDH/MYCN-amplified | Initial presentation Sites: treatment | First recurrence Time from diagnosis: sites: treatment | Second and subsequent recurrence(s) Time from diagnosis: sites: treatment | Outcome (time from diagnosis) |
|-------------|--------|------------------|------------------|---------------------|--------------------------------------|--------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 31          | Male   | 1.5mos           | 285<sup>a</sup>/34<sup>b</sup> | yes                | L Adr, BM, liver, skin: Cy(×3), RT, S | 1yr10mos: RP, B, BM, liver, P/E/Dox(×4), BMT, CRA | 3yrs7mos: Pelvis, B, BM: N6(×7), RT, 3F8 | DoD (5yrs4mos)               |
| 32          | Female | 1yr 3mos         | .../.../no       |         | Th: Cy/Dox(×5), RT | 5yrs11mos: Th, BM: P/E(×1), CAV(×1), ICE(×1), RT, SCT | 7yrs7mos: Th, B, BM: To ≥ V × Cy(×5), ICE(×2), RT, S, N7(×3), 3F8, CRA, oral E(×1), P/To(×1) | Toxic death/PD (10yrs6mos) |
| 33          | Male   | 1yr 4mos         | 163/422/no       | no      | Th: S(×2)          | 3yrs1mo: Th: S(×3), N2(×3), P/E(×1) | 5yrs4mos: Th, BM: oral E(×1) | DoD (5yrs6mos)               |
| 34          | Male   | 4yrs 11mos       | .../.../no       |         | Mandible: RT       | 9mos: Mandible, neck: S, RT, COD(×25) | 8yrs5mos: B, BM: N7(×7), 11<sup>1</sup>-13F8 | Toxic death/CR3 (9yrs6mos) |
| 35          | Male   | 5yrs 3mos        | 117/655/no       | no      | L Adr, Th: CCG(×5), S, RT, SCT | 1yr9mos: RP: S, RT, CRA | 2yrs2mos: Pelvis, RP: Cy/To(×9) | AwD (5yrs8mos+)             |
| 36          | Female | 6yrs 8mos        | .../.../...      |         | R Adr: S, Cy/V(×4) | 3yrs1mo: RP: N4(×1), S, RT, BMT | 3yrs5mos: Th, B: N4(×1), S, P/E(×1), RT, BMT | Toxic death (8yrs4mos)        |
| 37          | Male   | 7yrs 11mos       | .../.../...      |         | L Adr: S, RT       | 3yrs8mos: RP: S | 3yrs1mos: RP, B: Cy(×1), P/E(×8) | DoD (41yrs5mos)             |
| 38          | Female | 8yrs 123/348/no  | 123/348/no       | no      | Pelvis, RP: N5(×4), P/E(×2), S, RT | 4yrs11mos: L sc: S | 6yrs6mos: L sc: S | CR5 (13yrs3mos+)             |

See abbreviations and ** footnote in Table 1.

<sup>a</sup> In normal range for age.
<sup>b</sup> MYCN amplification was present at recurrence but not at diagnosis.
3F8,33,34 targeted radiotherapy (RT) with 131I-3F8,31 and cis-retinoic acid,3 which induces cellular differentiation. Protocol-based local RT with hyperfractionated 21 Gy was administered at MSKCC.35

RESULTS

Patient Characteristics at Diagnosis

Ages at diagnosis were 1.5 months–8 years 9 months (median, 3 years 10 months). Primary sites were the left adrenal (n = 14), right adrenal (n = 6), midline retroperitoneal (n = 6), thorax (n = 7), and pelvis (n = 2); three patients had no known primary tumor. At diagnosis, 30 patients had classic Stage 4 NB with metastases in bones and/or BM (Tables 1 and 2) and 8 patients had atypical cases (Table 3). MYCN was amplified in 2 of 28 patients tested. At diagnosis, 11 of 19 patients tested had elevated levels of serum ferritin and 1 of 18 patients tested had levels of serum LDH above 1500 U/L.

Overview of Outcome and Treatment

Among the 30 patients with classic Stage 4 NB, 21 had prolonged survival after a relatively early first recurrence of disease (1 year 1 month–3 years 10 months from initial diagnosis; Table 1) and 9 patients had very late first recurrences (4 years 3 months–13 years from diagnosis; Table 2). Among the eight patients with atypical cases, six had very late first recurrences in distant sites (4 years 11 months–8 years 8 months from diagnosis; Table 3). Nineteen patients were off therapy continuously for 3 or more years before experiencing a first or second recurrence. Twelve patients survive at 5 years 6 months+ to 19 years 4 months+ (median, 6 years 10 months+), including four in CR. Twenty-six patients died of disease (n = 22) or toxicity (n = 4) 5 years–41 years 5 months from diagnosis (median, 6 years 5 months).

Myeloablative chemotherapy was used to consolidate a first or second response in 27 patients. Highdose conventional chemotherapy helped achieve a second remission in 9 of 20 patients assessable for response of first recurrence but achieved no major response of second or third recurrences in 10 of 11 patients. The combination of multiple cycles of chemotherapy with modest toxicity, including oral etoposide and topotecan with/without cyclophosphamide (n = 21), anti-GD2 immunotherapy and/or cis-retinoic acid (n = 28), and targeted radiotherapy with 131I-MIBG or 131I-3F8 (n=11) helped prolong survival.

Patients with Classic Stage 4 Disease and Very Late First Recurrence

Initial chemotherapy regimens achieved first remission (PR or better) in 19 of the 21 patients in this subgroup; two patients (Patients 15, 19) required prolonged therapy to achieve first remission (Table 1). Treatments to consolidate first remission included myeloablative therapy in 12 patients, intensification of conventional chemotherapy in 6 patients, no additional therapy in 2 patients (Patients 10, 21), and 3F8 in 1 patient (Patient 12). Four patients also received cis-retinoic acid.

Among these 21 patients, first recurrences occurred 1 year 1 month–3 years 7 months (median, 2 years 11 months) from diagnosis and involved BM and/or bone in 18 patients and soft tissue alone in 3 patients. High-dose chemotherapy and/or myeloablative therapy achieved second remissions in nine patients (Patients 1, 2, 5, 8, 11, 12, 18, 20, 21) and no major responses in four patients (Patients 6, 14, 16, 17). Low/moderate-dose chemotherapy alone or in combination with anti-GD2 immunotherapy was associated with prolonged survival of two (Patients 13, 19) and six (Patients 4, 7, 9, 10, 15, 17) patients, respectively. 3F8 was used to consolidate CR2 in three patients (Patients 9, 20, 21) and, among patients with refractory BM disease, achieved CR2 in three patients (Patients 4, 14, 16) but not in two other patients (Patients 6, 17).

Second recurrences involved BM and/or bone in 18 patients and soft tissue alone in 3 patients. Two of these three patients were treated with surgery alone: Patient 17 had PD in BM/bone by 4 months but Patient 20 remained in CR3 for 1 year 3 months before another recurrence of disease. Among the 18 patients with widespread second recurrences, high-dose chemotherapy eradicated BM disease in Patients 12 and 18, but not in Patient 10; low/moderate-dose chemotherapy (after a second and/or third recurrence) was associated with the prolonged survival of 12 patients (2, 5–11, 13, 14, 16, 19); 3F8 was ineffective in one patient (Patient 3); and four patients (1, 15, 17, 21) died of PD within 7 months of the second recurrence.

Patients with Classic Stage 4 Disease and Early First Recurrence

Initial chemotherapy regimens achieved first remission (PR or better) in six of the nine patients in this subgroup; three required intensified (Patients 22, 29) or more prolonged (Patient 27) therapy to achieve remission (Table 2). First remission was consolidated by myeloablative therapy in five patients, intensification of conventional chemotherapy in one patient (Patient 26), no additional therapy in three patients (Patients 24, 29, 30), and cis-retinoic acid in three patients (Patients 25, 26, 28).

First recurrences were widespread (BM/bone) in five patients and were localized (three skull, one ret-
roperitoneal) in four. The patient (Patient 27) with the longest time to recurrence in this group (13 years) had a less than PR to intensive reinduction but the other eight patients achieved second remission (PR or better) with local control measures plus moderate-dose (Patients 22, 24) or high-dose chemotherapy (Patients 25, 26, 29), or high-dose chemotherapy followed by 3F8 (Patients 23, 28, 30). Three patients remain in CR2, including one (Patient 29) who has been off all treatment for 10 years 8 months+ and two who continue on therapy (Patients 26, 30).

Patients with Atypical Cases

Eight patients did not present with classic Stage 4 NB: Patient 31 had Stage 4S; Patients 32, 33, 36, and 37 had locoregional NB; Patient 32 had a mandibular lesion but no other detectable NB; and Patients 35 and 38 had Stage 4-N (Table 3).16

Initially, the five non-Stage 4 patients and the patient with detectable NB limited to the mandible were treated conservatively with low-dose chemotherapy, surgery, and/or RT: Patients 31 and 32 had widespread NB at first recurrence, achieved second remissions that were consolidated by myeloablative therapy but subsequently had chemoresistant recurrences; Patient 33 had a paraspinal/epidural tumor that was surgically debulked repeatedly and was resistant to high-dose therapy; Patient 34 achieved remission with RT and moderate-dose chemotherapy, but had a widespread recurrence 6 years 2 months after completion of treatment; Patient 36 received multimodality therapy for locoregional recurrences, developed a bony metastasis more than 7 years from diagnosis, and died of chemoresistant disease; and Patient 37 had an extremely late recurrence (39 years 1 month) that was resistant to moderate-dose chemotherapy. No major responses were seen in the four patients (Patients 31, 32, 33, 36) who received high-dose conventional or myeloablative chemotherapy for second recurrences.

Patient 33 was the only one of more than 45 patients with localized NB and no MYCN amplification who had a late recurrence after being treated at MSKCC with surgery alone. Aside from a serum ferritin level of 163 ng/mL, well established biologic prognostic factors in this patient were favorable,1,2 including less than 10 MYCN copies, Shimada pathology, DNA index 1.5, intact chromosome 1p, urine VMA:HVA ratio higher than 1, and serum LDH level of 422 U/L. This patient’s tumor had loss of heterozygosity of chromosome 19q, an abnormality that in preliminary studies is an adverse prognostic marker.36

The two Stage 4-N patients (Patients 35, 38) had multiple recurrences in distant lymph nodes but have not developed BM or bone metastases. Their first recurrences were managed conservatively (surgery, RT, and cis-retinoic acid in one, surgery alone in the other). Subsequent recurrences were extensive (rendered resectable by chemotherapy) in Patient 35 but small and readily resectable in Patient 38.

DISCUSSION

Our series of 38 patients who had metastatic NB present 5 years or more from diagnosis highlights the possibility of indolent or smoldering metastatic NB in children, as previously described in adolescents/adults.7 This phenomenon of chronic NB is rare with MYCN-amplified disease. Similar to our experience with children in the current study, MYCN amplification was identified in only 1 of 32 adolescents tested in the largest study to date of NB in older patients.7 Chronic NB may also be rare in patients who present with serum LDH levels above 1500 U/L.

Through the 1980s, deaths from NB were usually early events: less than 5% occurred beyond 3 years from diagnosis and less than 1% occurred after 5 years.9,37–40 Survival for more than 30 months after recurrence of Stage 4 NB was the exception, even with myeloablative retrieval therapy.41 Late recurrences also were rare. A report in 1990 added five cases to the 25 cases of recurrence after 5 years in remission that were already reported in the literature.12 The European Neuroblastoma Study Group provided the sole report to date that addressed the outcome of long-term survivors: among children with Stage 4 NB diagnosed between 1982 and 1990, a cohort with a 5-year event-free survival of 16%,40 9 of 75 in first and four of eight in second remission 5 years later had recurrence of disease (subsequent outcome was not presented) and all five patients with PD at 5 years later died of NB.14

Several developments in the 1990s may lead to an increased incidence of chronic NB. First, prolonged survival can be realized in patients with disease recurrence by using new chemotherapy regimens that have modest toxicity, are active against NB, and are well tolerated by patients who have been heavily pretreated. Such regimens include oral etoposide,19,20 and topotecan with/without cyclophosphamide,18,25,26 and are compatible with many normal childhood activities. Second, emerging biologic therapeutic agents such as cis-retinoic acid,3 fenretinide,42 anti-GD2 MoAbs,33,34,43 and antiidiotype vaccines44–46 may prove effective in achieving or consolidating remissions. In addition, these agents are generally accepted as being nontoxic to children. Longer follow-up of children with NB is needed to determine whether these regimens will merely retard NB growth (and
thereby increase the incidence of late recurrences) or will actually improve cure rates. Third, targeted RT using 
$^{131}$I-MIBG or $^{131}$I-3F8 may provide more effective and less toxic treatment than conventional external-beam RT. Finally, an increase in late recurrences of Stage 4 NB already appears to have resulted from the use of myeloablative consolidation. A further increase may follow the widespread use of more dose-intensive induction regimens that, combined with surgery and local RT, may improve response rates and reduce tumor burdens.

Previous reports described the efficacy of low-dose chemotherapy in Stage 4 patients who experienced disease recurrence after being off treatment for more than 1 year and the poor response of myeloablative therapy Stage 4 NB that recurs within 1 year of diagnosis. Presumably, early PD reflects highly resistant NB that cannot be arrested sufficiently to allow prolonged survival. Our experience supports that concept: only two patients (Patients 5, 13) had PD within 1 year of completing consolidative conventional or myeloablative chemotherapy; retrieval chemotherapy produced PR or better in more than 40% of patients with first recurrences; and low/moderate-dose therapy proved beneficial in terms of tumor control in 21 patients.

Among patients with Stage 4 NB, those with isolated lymph node metastases comprise a distinct subset. Patients with Stage 4-N disease, in the absence of MYCN amplification, have a better prognosis than patients with classic Stage 4 disease. Our two Stage 4-N patients have had prolonged survival with more than one recurrence of soft tissue disease but no spread to BM/bones. In a similar case, the patient died of toxicity 14 years after diagnosis. The tendency of Stage 4-N disease to stay confined to soft tissue, the small chance that chemotherapy will definitively prevent subsequent recurrences, and the risk of excessive cumulative toxicity from repeated use of chemotherapy are factors to be weighed when these patients experience disease recurrence. Chemotherapy was needed in one of our Stage 4-N patients to allow resection of relapsed NB. However, the small size of the successive lymph node recurrences in our other Stage 4-N patients allowed management with repeated surgery alone. Biologic therapies may be an alternative consolidation measure in this subgroup of patients.

Late recurrence can be a vexing problem. Early reports placed recurrence after apparent cure in the context of the “enigmatic” nature of NB. The four patients (Patients 32, 33, 36, 37) in our series who presented initially with localized NB had distant recurrences more than 3 years from diagnosis. Recurrences in BM/bone are rare events with localized NBs that have favorable biologic prognostic markers and occur most often within 1 year of diagnosis. Since the 1980s, however, recurrence after apparent cure has frustrated investigators who use myeloablative therapies to consolidate CR in patients with classic Stage 4 NB. This problem is strikingly illustrated by the recurrence of NB more than 10 years posttransplant in Patient 27 in our series. The plasticity of NB cells in culture, with transformation from the highly proliferative N-type cell to the more dormant S-type, may provide a biologic basis for prolonged CR followed by recurrence. Nevertheless, late recurrence after 4 years of remission has not occurred among patients consolidated with the 3F8 anti-GD2 MoAb.

We conclude that although its complete eradication (cure) is uncommon, recurrence of Stage 4 NB in children can be arrested for long periods of time, often using therapies of modest toxicity. Prolonged survival following multiple recurrences is possible. The coming decade will reveal the impact (on survival and cure rates) of complex therapeutic programs that incorporate novel treatments developed in the past 10–15 years, including dose-intensive induction chemotherapy, aggressive local control measures, myeloablative therapy, and various biologic therapies for consolidation of disease remission.

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