**MYCN-amplified stage 2/3 neuroblastoma: excellent survival in the era of anti-G\(_{D2}\) immunotherapy**

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**Keywords:** neuroblastoma; anti-G\(_{D2}\) antibody; autologous transplantation; cytokine; MYCN amplification

**Received:** May 07, 2017  **Accepted:** August 07, 2017  **Published:** August 24, 2017

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**ABSTRACT**

High-risk neuroblastoma (HR-NB) includes MYCN-amplified stage 2/3, but reports covering anti-G\(_{D2}\) immunotherapy, which recently became standard for HR-NB, do not provide details on this subset. We now report on all 20 MYCN-amplified stage 2/3 patients who received induction chemotherapy at our center during the era of consolidation with anti-G\(_{D2}\) antibody 3F8/ granulocyte-macrophage colony-stimulating factor (GM-CSF) (2000-2015). Early in this period, consolidation included autologous stem-cell transplantation (ASCT). Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan-Meier analyses.

With induction, 19/20 (95%) patients achieved complete/very good partial remission (CR/VGPR) but one had progressive disease with early death. One responder did not receive consolidation and died of relapse. Five-year post-diagnosis EFS/OS rates for all 20 patients were 72%/84%. The 18 CR/VGPR patients who received consolidation had EFS/OS 81%/94% at five years from starting 3F8/GM-CSF: 4/4 ASCT patients remained relapse-free, while 11/14 non-ASCT patients remained relapse-free and two of the three relapsed patients achieved 2\(^\text{nd}\) CR (consolidated by retreatment with 3F8/GM-CSF) and remained in 2\(^\text{nd}\) CR at 36+ and 95+ months post-relapse. The 14 non-ASCT patients had EFS/OS 73.5%/93% at five years from starting 3F8/GM-CSF.

This subset appears to have a good prognosis with contemporary multi-modality therapy, possibly even without ASCT.

**INTRODUCTION**

High-risk neuroblastoma (HR-NB) has long included MYCN-amplified stage 2 or 3 disease [1]. Because this entity is found in <10% of NB patients [1], the literature on this subset is limited [2–15], with the largest reported group-wide studies including 12-to-32 patients [4-6, 8-14]. Only one report covers this subset exclusively [9]. Other reports use definitions of MYCN amplification that are no longer accepted (MYCN copy number \(\geq 3\) [8, 10, 12] or various threshold values [13]). Analysis is further hampered because several reports, [4-8, 10-12, 16, 17] in presenting outcome data, group these patients with MYCN-amplified stage 1, MYCN-amplified stage 4S, and/or MYCN-non-amplified stage 3 (which we reported has an excellent outcome when treated by surgery alone at diagnosis [18]). Further, therapy for low-stage MYCN-amplified NB has varied widely from surgery alone [13] to myeloablative therapy with autologous stem-cell transplantation (ASCT) [9, 11, 13, 16]; details of treatment were not provided in the largest cohort of stage 3 reported to date [15].
With conventional chemotherapy alone, MYCN-amplified stage 2/3 patients typically relapsed in the primary as well as in distant sites [2-4, 7-9, 14]. ASCT plus local radiation therapy (RT) improved outcome in a small series (n=12), [9] but ASCT did not improve event-free survival (EFS) or overall survival (OS) of either MYCN-amplified stage 2 patients (n=39) collected by the International NB Risk Group (INRG) [13] or stage 3 patients (n=72) deemed high risk (including MYCN-non-amplified disease) in a national study [14]. Other reports concerning ASCT + RT do not provide outcome data on MYCN-amplified stage 2/3 [11, 16].

Anti-GD2 antibodies such as dinutuximab and 3F8 are active against HR-NB [19]. Although no study compares efficacy, it is reasonable to assume approximately comparable anti-NB activity of different anti-GD2 antibodies. Immunotherapy using these agents recently became standard for HR-NB. However, reports showing a benefit do not include [20], or do not provide details on [21], stage 2/3 patients. We reported on stage 4 HR-NB treated at Memorial Sloan Kettering (MSK) with 3F8 alone [22] or plus granulocyte-macrophage colony-stimulating factor (GM-CSF) [23]. We now present results with MYCN-amplified stage 2/3.

Since 1990, the MSK treatment program for HR-NB has included dose-intensive chemotherapy [24, 25] and tumor resection [26] for induction, followed by consolidation using 3F8 [23] and local RT [27]. We added ASCT and isotretinoin for consolidation in 2000 after those treatments were reported as beneficial, [28] but we discontinued ASCT (though not isotretinoin) in 2003 because published ASCT studies [29-31] showed no survival advantage compared to the earlier MSK non-ASCT programs that used 3F8 without cytokines [22, 23]. We found no significant difference with or without ASCT in EFS or OS of stage 4 HR-NB patients in CR consolidated with 3F8/GM-CSF+isotretinoin plus local RT [23, 32]. We now report excellent outcome of MYCN-amplified stage 2/3, with or without ASCT.

RESULTS
Patient characteristics

The 20 patients (male:female, 11:9) had features typical of MYCN-amplified stage 2 (n=2) or stage 3 (n=18) HR-NB, including young age (10-75 [median 25] months), abdominal site, predominance of unfavorable histology, and elevated serum levels of lactate dehydrogenase at diagnosis (Table 1).

Overview of outcome of the entire cohort

Of the 20 patients (Table 1), 19 (95%) achieved CR/VGPR with induction while one patient (#2) had PD with induction and died of PD at 6.5 months post-diagnosis. One CR patient (#1) received no consolidation (social reasons), had a widespread relapse documented at 18 months, and, despite aggressive salvage therapy, died of PD at 36 months post-diagnosis. The other 18 CR/VGPR patients received consolidation with 3F8/GM-CSF+isotretinoin+RT, including four with and 14 without prior ASCT. Minimal residual disease (MRD) was negative before 3F8/GM-CSF in 17 patients and positive in only one patient (#20), and was negative in all 18 patients after 2 cycles of this immunotherapy. The number of patients with either favorable histology (n=3) or an ALK mutation (n=3) was too small to assess for possible prognostic significance (Table 1). At 5 years from diagnosis, the entire cohort of 20 patients had EFS 72% ± standard error 11% and OS was 84% ± 9% (Figure 1).

Five patients had pathologic CR at 2nd-look surgery (Table 1) including the sole CR patient (#1) who did not receive consolidation and eventually relapsed (see above), and four non-ASCT patients, two of whom relapsed (patients #14 and #15). With thoraco-abdominal explorations, gross total resections were achieved at 2nd-look surgery in all but one patient (#20; ~80% resected, to avoid injury to portal vein and pancreatic ducts). Surgical complications included nephrectomy (patient #5), cholecystectomy for gall bladder obstruction (patient #13), hypertension from renal vasculature insufficiency (patient #14), and recurrent pleural effusions (patient #18). No unexpected chemotherapy-related complications occurred.

Outcome of patients consolidated with 3F8/GM-CSF+isotretinoin

At five years from the start of 3F8/GM-CSF, the EFS and OS rates of the 18 patients whose CR was consolidated with 3F8/GM-CSF+isotretinoin+RT were, respectively, 81% ± 10% and 94% ± 5% (Figure 2A). All four ASCT patients remain in CR at 145-206 (median 199) months from diagnosis, including the only patient (#20) with MRD detected in bone marrow (BM) pre-3F8/GM-CSF (MRD was negative when re-assessed after cycle 2 of 3F8/GM-CSF).

Eleven of the 14 non-ASCT patients remain relapse-free at 24-162 (median 60) months from diagnosis and 19-156 (median 55) months from the start of 3F8/GM-CSF, including four who received additional consolidative adjuvant (experimental and unproven) therapy with DFMO [33] (n=1) or a vaccine [34] (n=3). Two of the three patients who relapsed – one early at 10 months and one late at 59 months from diagnosis, both only in soft tissue outside the RT fields – have achieved prolonged ongoing continuous 2nd CRs (95+ months for patient #14, 36+ months for patient #15). Their successful salvage therapy included previously described 2nd-line chemotherapy regimens, [35-37] resection of relapsed tumor, and local RT (21 cGy [26]). They also received repeat treatment with 3F8/GM-CSF+isotretinoin to consolidate their 2nd...
Table 1: Clinical and biological features

| Patient #/sex/age at Dx/stage/site | LDH (U/L) | Ferritin (ng/mL) | ALK | Histology | Pathology at 2nd-look surgery | Outcome (time from Dx) |
|-----------------------------------|-----------|------------------|-----|-----------|-------------------------------|-----------------------|
| A. Patients without consolidative therapy | | | | | | |
| **Complete remission with induction but no subsequent consolidation** | | | | | | |
| 1/M/32m/3/RP | 5300 | 74 | F1174L | … | (-) | PD (abd, bones) at 18m. Dod at 36m |
| **PD with induction** | | | | | | |
| 2/M/19m/3/R Adrenal | … | 169 | Wild type | UH | (+) | PD (abd) at 5m. Dod at 6.5m |
| B. Non-ASCT patients with 1st remission consolidated by 3F8/GM-CSF, radiotherapy, and isotretinoin | | | | | | |
| **Patients in continuing CR** | | | | | | |
| 3/F/10m/3/L Adrenal | 3958 | 197 | … | UH | (+) | CR at 162m |
| 4/M/54m/3/RP | 1637 | 111 | Wild type | UH | (-) | CR at 100m |
| 5/M/25m/3/L Adrenal | 1510 | 185 | Wild type | UH | (+) | CR at 99m |
| 6/F/37m/2/L Adrenal | 2789 | 52 | … | UH | … | CR at 92m |
| 7/M/18m/3/L Adrenal | 2051 | 175 | Wild type | FH | (+) | CR at 84m |
| 8/F/59m/3/L Adrenal | 1953 | 461 | Wild type | UH | (+) | CR at 61m |
| 9/M/48m/2/L Adrenal | 401 | … | Wild type | UH | (+) | CR at 43m |
| 10/F/25m/3/RP | 2102 | … | R1275L | UH | (-) | CR at 34m<sup>a</sup> |
| 11/M/14m/3/R Adrenal | 968 | … | Wild type | UH | (+) | CR at 28m<sup>b</sup> |
| 12/M/75m/3/R Adrenal | 4955 | … | Wild type | UH | (+) | CR at 26m<sup>b</sup> |
| 13/M/15m/3/R Adrenal | 2619 | 166 | Wild type | UH | (+) | CR at 24m<sup>b</sup> |
| **Patients who relapsed** | | | | | | |
| 14/M/31m/3/L Adrenal | 2000 | … | Wild Type | UH | (-) | PD (pelvis) at 59m. 2nd CR 94m from relapse |
| 15/F/47m/3/L Adrenal | 624 | … | F1174L | UH | (-) | PD (thorax) at 10m. 2nd CR 34m from relapse |
| 16/M/13m/3/L Adrenal | 872 | 448 | Wild Type | FH | (+) | PD (abd) at 10m. Dod at 13m |
| C. ASCT patients with 1st remission consolidated by 3F8/GM-CSF, radiotherapy, and isotretinoin | | | | | | |
| 17/F/51m/3/RP | 600 | … | … | UH | (+) | CR at 206m |

(Continued)
CRs, as described [38], plus additional immunotherapy using a vaccine [34]. The other relapse was early, at 10 months, in soft tissue within the RT field, followed three months later by death from PD (patient #16). Overall, this cohort of 14 non-ASCT patients had EFS 73.5% ± 14% and OS 93% ± 7% at 5 years from the start of 3F8/GM-CSF (Figure 2).

As previously noted [23], 3F8/GM-CSF had manageable toxicities – hence, treatment was outpatient for the non-ASCT and the ASCT patients. 3F8 caused grade 1-2 generalized pain and urticaria but no unexpected toxicities [23, 32]. The only grade 3 toxicity of 3F8/GM-CSF was transient hypertension in the 1st cycle of one

| Patient #/sex/age at Dx/stage/site | LDH (U/L) | Ferritin (ng/mL) | ALK | Histology | Pathology at 2nd-look surgery | Outcome (time from Dx) |
|-----------------------------------|----------|------------------|-----|-----------|-----------------------------|-----------------------|
| 18/F/22m/3/L Adrenal              | 8189     | …                | …   | …         | (+)                          | CR at 202m             |
| 19/F/18m/3/RP                     | 2642     | 125              | …   | FH        | (+)                          | CR at 195m             |
| 20/F/19m/3/RP                     | 613      | 154              | Wild type | UH       | (+)                          | CR at 145m             |

abd, abdomen; ASCT, autologous stem-cell transplantation; Dod, died of disease; Dx, diagnosis; F, female; FH, favorable histology; LDH, lactate dehydrogenase; M, male; PD, progressive disease; RP, retroperitoneal; UH, unfavorable histology.

a Started difluoromethylornithine (DFMO)\(^3\) after completing 3F8/GM-CSF+isotretinoin.
b Started vaccine\(^3\) after completing 3F8/GM-CSF+isotretinoin.

![Figure 1: EFS and OS of all 20 patients.](os_doiz.png)
patient (#13). Common side-effects of isotretinoin were grade 1-2 dry skin and cheilitis.

DISCUSSION

This report is the first to focus on MYCN-amplified localized NB in the era that began when anti-G<sub>D2</sub> immunotherapy became standard of care for HR-NB. This period coincided with the routine use of dose-intensive induction and consolidation with local RT and isotretinoin for HR-NB. Regarding MYCN-amplified stage 2/3, our experience shows that 1) dose-intensive chemotherapy and surgery can achieve a high CR rate, and 2) excellent long-term survival is associated with consolidation using anti-G<sub>D2</sub> antibody, isotretinoin, and RT. The 5-year EFS/OS rates of 72%/84% (Figure 1) might have been even better had one patient (#1 in Table 1) received consolidation after achieving CR with induction. This child’s relapse, despite a complete pathologic response documented at 2<sup>nd</sup>-look surgery, underscores the importance of consolidative measures.

In past reports on HR-NB [23, 32], we assessed multiple prognostic markers in univariate and multivariate analyses, but in the current study the low number of events precluded the utility of prognostic markers. Nevertheless, it would appear that for this subset of patients there is the same lack of survival advantage with ASCT as seen in our entire cohort of HR-NB patients [23, 32]. Of note, since 1988, our definition of HR-NB has not included MYCN-non-amplified localized (including stage 3) disease which we have managed upfront with surgery alone [18].

Four of the long-term survivors received DFMO or vaccine (patients #10-13 in Table 1) after completing antibody treatment. These investigational therapies are of unproven benefit for HR-NB; it cannot be certain whether their use improved outcome. If efficacy is ultimately confirmed with more data in ongoing formal clinical trials, then either or both might be incorporated into the standard of care for HR-NB.

The MSK results with MYCN-amplified stage 2/3 are comparable to the 6-year EFS/OS rates of 83%/83% in the series of 12 similar patients whose consolidation included ASCT+RT, though not anti-G<sub>D2</sub> antibody or isotretinoin, as presented in the only other report focused specifically on this subset of patients [9]. These EFS/OS rates in turn are better than those in other reports with data on MYCN-amplified stage 2/3 treated with conventional chemotherapy ± RT, including 5-year EFS/OS 32%/36% (n=22) [4] and 6-year OS 25% (n=20) [9] in early French studies, and 1/12 (8%) patients surviving in the Italian experience [8].

Inferior results compared to the current MSK report and the French ASCT+RT experience [9] were also seen in the only two published studies with data on ASCT in high-risk stage 2 or 3. Thus, the CCG-3891 trial which involved randomizations of ASCT and isotretinoin, but not routine use of local RT, showed 5-year EFS/OS rates of 25%/25% for MYCN-amplified stage 3 (n=24); neither ASCT nor isotretinoin had a significant impact on outcome for the entire stage 3 cohort (n=72), which included MYCN-non-amplified disease [14]. In that report, the “overall poor prognosis” led the authors to note that “[f]urther studies are warranted to determine if myeloablative consolidation followed by 13-cis-RA maintenance therapy statistically significantly improves outcome.” Similarly, ASCT did not improve survival in the INRG cohort of MYCN-amplified stage 2 NB (n=39, including nine ASCT), with 5-year EFS/OS of 57%/67% [13].

Reports on more recent large studies of HR-NB do not include patients with MYCN-amplified stage 2/3.

![Figure 2: Patients in complete remission treated with 3F8/GM-CSF+isotretinoin.](image-url)

EFS and OS of: (A) all 18 patients, and (B) the 14 non-ASCT patients.
may now supersede EFS endpoints as recent developments offer hope that the equivalence between relapse and lethality may no longer hold true. Thus, as in our two patients, close monitoring [48] can detect localized relapses [23], which might be controlled by surgery and/or focal RT, supplemented by systemic therapies that are non-cross-resistant with prior treatments. Examples include chemotherapy regimens [37, 50] and novel agents [33, 51]. Consolidation of 2nd CR in our two patients included retreatment with 3F8/GM-CSF+isotretinoin, as previously reported [38]. They also received a vaccine used with oral β-glucan; this immunotherapy has shown promise in consolidating 2nd CR [34].

In conclusion, a cautious interpretation of the MSK experience is that ASCT may not be warranted when local RT, anti-G_{123} antibodies, and isotretinoin are used for consolidation after dose-intensive induction chemotherapy. This possibility is supported by a critical review of ASCT for HR-NB reaching back 30 years [45], the loss of long-term survival advantage with ASCT for stage 3 and 4 in a major randomized study [17], and the absence of a benefit with ASCT for localized HR-NB [13, 14]. A definitive confirmation that ASCT does not improve outcome would require a prospective randomized trial. Discontinuing ASCT for HR-NB would be consistent with the general consensus among pediatric oncologists that this highly toxic treatment is no longer recommended for all other extracranial pediatric solid tumors [43, 44].

MATERIALS AND METHODS

This report covers all MYCN-amplified stage 2/3 patients who received induction [24, 25] at MSK during the era of immunotherapy with 3F8/GM-CSF (2000-2015) [23, 32]. Stage and MYCN amplification were defined by international criteria [52, 53]. ASCT post-induction was standard through 2003 [16, 54]. Consolidation included local RT (21 Gy) [27] applied between the 1st and 2nd cycles of 3F8/GM-CSF, with 3F8 at 100 mg/m²/cycle, as described [23, 32]. Isotretinoin was taken orally (x6 courses, as described[57]) between cycles of 3F8/GM-CSF, beginning after the 2nd cycle [23, 32]. Informed written consents for all treatments were obtained according to institutional review board rules.

Extent-of-disease evaluations included \(^{123}\)I-metiodobenzylguanidine (MIBG) scan and computed tomography or magnetic resonance imaging of chest-abdomen-pelvis every 3 months. BM aspirates and biopsies obtained from bilateral posterior and anterior iliac crests were studied by histology every 3-6 months. Disease status was defined by the International NB Response Criteria [52], modified to incorporate \(^{123}\)I-MIBG findings. CR: no evidence of NB, including normal \(^{123}\)I-MIBG scan and BM(-) by histology. VGPR, primary mass reduced by 90%, and no evidence of distant disease in soft tissue.
bones, or BM; and PD: new lesion or >25% increase in an existing lesion.

Quantitative reverse transcription-polymerase chain reaction was used, as described [23], to assess MRD in BM before the initiation of immunotherapy and then after the 2nd cycle of 3F8/GM-CSF.

EFS and OS were estimated using Kaplan-Meier analyses, calculated from diagnosis or from the start of 3F8/GM-CSF. Events were defined as relapse, secondary neoplasm, or death. OS was defined as time to death or last follow-up.

Abbreviations

HR-NB, high-risk neuroblastoma; ASCT, autologous stem cell transplant; EFS, event free survival; RT, radiation therapy; OS, overall survival; CR/VGPR, complete remission/very good partial remission; MSK, Memorial Sloan Kettering Cancer Center; GM-CSF, granulocyte-macrophage colony-stimulating factor; BM, bone marrow; MRD, minimal residual disease.

Author contributions

BHK MPL, SM, SLW, EMB, SSR, KK, KY, IYC, NKVC critically reviewed, revised, and approved the final manuscript. BHK, NKVC, SM, EMB, SSR, KK, KY, IYC and NKVC analyzed and interpreted data. BHK, MPL, SM, SLW, EMB, SSR, KK, KY, IYC, NKVC collected and assembled data. BK, NKVC conceived and designed the study.

ACKNOWLEDGMENTS

We wish to thank Joe Olechnowicz for editorial assistance.

CONFLICTS OF INTEREST

Antibody 3F8 was licensed to Ymabs Inc. by Memorial Sloan Kettering Cancer Center (MSK). MSK and NKC have financial interest in Ymabs.

FUNDING

This work was supported in part by the Core Grant (P30 CA008748) and by grants from the National Institutes of Health (CA106450), Bethesda, MD; the Robert Steel Foundation, New York, NY; Katie’s Find A Cure Fund, New York, NY; and the Arnold J. Jacobs Pediatric Cancer Fund, New York, NY.

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