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Recurrent Neuroblastoma

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1. Introduction

Advances in neuroblastoma (NB) treatment over the last three decades have resulted in our ability to cure over 70% of children with NB using the current risk-directed therapeutic approach. However, until very recently, improvement in treatment outcome was mainly attributable to the increased survival of low and intermediate-risk patients. The outcome of high-risk NB, especially in children older than 18 months with metastatic disease, remains poor. Despite intensive multimodal therapy, over 50% of patients with high-risk NB relapse with a dismal long-term outcome (Lau et al., 2004; Santana et al., 2008). While immunotherapy has recently increased the post-transplant 2-year event-free survival (EFS) of high-risk NB from 46% to 66% (Yu et al., 2010), longer follow-up is required to monitor for late relapse.

In the last era, children with NB have been offered a wide variety of salvage treatments following disease recurrence. Up to half of these patients achieve some response or stable disease, and survival after relapse is longer in patients who have received salvage therapy (Lau et al., 2004). Chronic NB is also an emerging phenomenon in a subset of patients (Kushner et al., 2002). The longer survival after relapse is also likely due to early detection of disease recurrence as a result of employing more sophisticated surveillance studies in recent years. Furthermore, a proportion of relapsed patients are offered novel agents in phase I/II clinical trials. Unfortunately, response to any form of relapsed therapy is rarely sustained. Future research leading to a better understanding of the factors influencing the clinical course of post-relapse is therefore very important, such that clinicians can select the appropriate salvage therapy: to avoid intensive toxic treatment in patients likely to have short survival following disease recurrence and to test potentially beneficial therapy.

2. Clinical presentation of recurrent NB

Similar to NB at initial diagnosis, the signs and symptoms of relapsed NB reflect the site of local and metastatic disease. However, due to the high frequency of metastatic disease at the presentation of relapse, symptoms and signs related to distant metastases are significantly more common than at diagnosis. Isolated metastatic relapse is found in 60% of patients, followed by combined locoregional and metastatic relapse in 32% of patients (Table 1; (Lau et al., 2004). Isolated local relapse at the primary tumor site is uncommon (6%) and is

generally confined to patients with non-metastatic disease at diagnosis. Bone and/or bone marrow disease are present in 75 to 85% of patients with recurrent disease (Kushner et al., 2002; Lau et al., 2004). As a result, bone pain from osteomedullary metastases represents the most common presenting symptom and is reported by 68% of patients with symptomatic relapse (Lau et al., 2004). Other symptoms from distant metastases include lethargy, irritability, soft tissue mass arising from bony involvement of the calvarium, periorbital ecchymosis (raccoon eye), pallor and bruising from bone marrow infiltration and cytopenia, and soft tissue mass from lymph node metastases. Depending on the frequency of follow-up and the type of investigations used to monitor relapse, 30 to 73% of patients are asymptomatic at relapse (Kushner et al., 2009; Lau et al., 2004).

Type of relapse	
Local only	2
Metastatic only	19
Local and metastatic	10
Site of distant relapse	
Bone, bone marrow +/- others	16
Bone and non-bone marrow	6
CNS and bone marrow	1
Bone marrow only	1
CNS only	2
Lung only	2
Lymph node only	1
Symptoms/Signs	
Yes	22
No	9
Time from diagnosis to relapse	median 16.1 months (1.7 – 35.8 months)
Survival post relapse	median 8.4 months (0.2 - 51.1 months)
1-year OS	39%
3-year OS	11%

Table 1. Characteristics of 31 relapsed NB patients from a single institution (Lau et al., 2004)

While central nervous system (CNS) disease is very rare at diagnosis, CNS recurrence has been reported in 1 to 5% of all patients with Stage 4 NB (Kellie et al., 1991; Kramer et al., 2001; Matthay et al., 2003a; Shaw & Eden, 1992). CNS metastases represent 6 to 10% of all disease recurrences and 50 to 70% of these CNS recurrences are isolated CNS relapse. This is thought to be related to prolonged survival of high-risk NB following intensive systemic therapy and the CNS as a sanctuary site for NB. Neuroaxis metastases can be intraparenchymal, leptomeningeal, or both. Patients can present with nausea, vomiting, headaches, seizures, drowsiness, cranial nerve symptoms, motor weakness/paralysis, and back pain (Matthay et al., 2003a).

Fifty percent of relapses present within 18 months from diagnosis and 77% by 24 months (Kushner et al., 2009; Lau et al., 2004; London & Castel et al., 2011; Santana et al., 2008). For CNS recurrence, the median time of relapse was 12 to 20 months (Kellie et al., 1991; Kramer et al., 2001; Matthay et al., 2003a; Shaw & Eden, 1992). Even though late relapse is uncommon, a small number of patients present with first disease recurrence after 5 years

and on rare occasions beyond 10 years from diagnosis. Cotterill et al. reported that amongst 406 patients who were in first remission five years from diagnosis, 3% subsequently relapsed and most late relapse patients had Stage 4 disease at diagnosis (Cotterill et al., 2001).

3. Risk of disease recurrence

The 'events' considered for analyses of EFS typically include relapse, progression, secondary malignancy, or death (from any cause prior to the detection of disease relapse or progression). In the majority of NB patients, the first event that patients experience is disease relapse or progression. Therefore, factors that are prognostic of EFS are the same risk factors that are prognostic for NB relapse. Established risk factors for relapse include older age at diagnosis, higher disease stage, *MYCN* amplification, DNA diploidy, and chromosome 1p and 11q aberration.

Since the early 1970's, age at diagnosis has been considered a useful factor in predicting the occurrence of first relapse, disease progression, or death (Evans et al., 1971), and has persisted as highly prognostic despite the discovery of new molecular prognostic factors over the last 30 years. Prior to 2005, an age cut-off of 12 months was used for risk group stratification. Since 2005, a cut-off of 18 months (547 days) has been adopted by the Children's Oncology Group (COG) (London et al., 2005) and was included in the International Neuroblastoma Risk Group (INRG) staging system in 2009 (Monclair et al., 2009). In INRG cohort of 8,800 patients, the 5-year EFS was 42% for patients ≥18 months, compared with 82% for patients <18 months old (Cohn & Pearson et al., 2009) (Table 2). The 5-year EFS for Stage 4 NB was significantly worse than that of non-Stage 4 disease (35% vs. 83%). For tumors with *MYCN* amplification, 11q aberration, 1p aberration, and DNA ploidy ≤ 1, the 5-year EFS were 29%, 35%, 38%, and 55%, respectively. Patients ≥18 months old with Stage 4 *MYCN* amplified NB had the worst outcome (5-year EFS of 19%). In contrast, in spite of Stage 4 disease, the 5-year EFS was 85% for Stage 4 patients younger than 18 months with tumor DNA ploidy >1. In relation to Stage 4S disease, *MYCN* amplification reduced EFS from 82% to 41%, and within the *MYCN* non-amplified group, 11q aberration decreased EFS from 86% to 38% (Ambros et al., 2009).

Moreover, in addition to disease progression on therapy, metastatic response to therapy measured by semi-quantitative metaiodobenzylguanidine (MIBG) score identifies a subgroup of ultra-high-risk patients. In a study of 75 patients, patients with MIBG score >2 after 4 cycles of induction therapy had significantly lower 5-year EFS than those with MIBG score ≤2 (11% vs. 39%) (Matthay et al., 2003b). A recent study of over 250 patients reported a 3-year EFS of 8.3% in patients with a MIBG score >5 post-induction, compared with EFS of 42% in patients with MIBG score ≤ 2 (Yanik et al., 2010). High ferritin levels in Stage 4 patients ≥18 months also reduced 5-year EFS from 48% to 21% for *MYCN* non-amplified tumors and from 28% to 19% for *MYCN* amplified tumors (Cohn & Pearson et al., 2009).

While the majority of disease recurrences occur in high-risk patients, a small percentage of relapsed patients had localized NB at diagnosis and subsequently present with local or metastatic relapse. Factors predictive of relapse in localized NB include the presence of image-defined risk factors (IDRF), tumor histology, *MYCN* amplification, 1q and 11q aberration, and ALK overexpression. In the INRG pretreatment risk classification system, patients with localized NB and IDRF (Stage L2; 5-year EFS of 78%) have significantly worse

outcome than those without IDRF (Stage L1; 5-year EFS of 90%) (Monclair et al., 2009). Non-Stage 4 patients with *MYCN* amplified tumors have a 5-year EFS of 46%, compared with *MYCN* non-amplified tumors with a 5-year EFS of 87% (Table 2). Within the *MYCN* non-amplified cohort, the EFS of patients with 11q aberration and/or undifferentiated histology is significantly lower than those without these features (61% vs. 80%)(Cohn & Pearson et al., 2009). Specifically, for patients with stroma-poor localized resectable tumors, the presence of 1q gain and absence of 7p gain may predict relapse (Pezzolo et al., 2009). Furthermore, high ALK protein expression, though uncommon, may be prognostic in Stage 1 and 2 patients. Six of eight Stage 1 and 2 patients with high wild-type ALK expression experience relapse (Parodi et al., 2011).

	5-year EFS ± SE (%)	
	Yes	No
Age ≥18 months	42 ± 1	82 ± 1
Stage 4	35 ± 1	83 ± 1
MYCN amp.		
all stages	29 ± 2	74 ± 1
non-Stage 4	46 ± 4	87 ± 1
Stage 4S	41 ± 9	82 ± 2
Stage 4 & age ≥18 months	19 ± 3	48 ± 5
Stage 4 & ploidy >1		85 ± 3
11q aberration		
all patients	35 ± 5	68 ± 3
non-Stage 4 & MYCN non-amp.	61 ± 11	80 ± 16
Stage 4S & MYCN non-amp.	38 ± 30	87 ± 7
1p	38 ± 3	74 ± 2
DNA ploidy ≤ 1	55 ± 2	76 ± 1

Table 2. EFS by prognostic factors in a cohort of 8,800 patients (Cohn & Pearson et al., 2009)

Furthermore, MYCN amplification, and lumbar puncture at diagnosis were found to be significant risk factors for CNS recurrences in a report of 434 Stage 4 NB patients (Matthay et al., 2003a). In another study of 251 Stage 4 patients, lumbar puncture and elevated serum lactate dehydrogenase (LDH) were reported to be risk factors (Kramer et al., 2001). In these two studies, 28% to 36% of the patients with CNS recurrence had a lumbar puncture during diagnosis. As for late relapse beyond 5 years, a multivariate analysis of 422 patients demonstrated a relative risk of 10.5 for late relapse in patients >12 months with Stage 4 disease at diagnosis, and a relative risk of 4.2 for those with prior relapse (Cotterill et al., 2001). For patients who remained in first remission 5 years from diagnosis, the 10-year progression-free survival (PFS) for patients >12 months with Stage 4 disease at diagnosis was lower for other children (88% vs. 98%).

3.1 Detection of disease recurrence
A multitude of follow-up studies have been used to detect disease recurrence. These include imaging with ultrasonography, computed tomography (CT), magnetic resonance imaging

(MRI), bone scan, MIBG scan and positron emission tomography (PET), as well as bone marrow examination and urine catecholamines. The choice of tests depends on whether the patient presents with symptoms and signs indicative of the location of relapse, and therefore guide the studies to be performed. However, when surveillance studies are undertaken to detect asymptomatic relapse, a number of factors including the risk of relapse, as well as the sensitivity/specificity, invasiveness, and the cost of the studies will need to be taken into consideration.

3.2 Locoregional disease

CT is commonly the test of choice for imaging locoregional recurrence in the thorax (Figure 1), abdomen, and pelvis (Brisse et al., 2011), especially in high risk patients who have received local radiotherapy, and the radiation dose from CT is relatively small compared with that from radiotherapy. For patients with low- and intermediate-risk NB, ultrasound of the abdominal and pelvic region could be considered the first imaging examination to avoid radiation exposure from CT, particularly when there is a low index of suspicion of relapse. MRI provides effective imaging without radiation, but it is limited by availability, cost, and the need for sedation in young children. However, for paraspinal tumors with intraspinal extension, MRI is recommended for better visualization of the spinal cord, nerve roots, and the subarachnoid space (Sofka et al., 1999). MIBG scintigraphy, which is routinely used to detect osteomedullary recurrence, will also demonstrate local recurrence (Figure 1).

3.3 Metastatic disease

Detection of metastases is an integral component of monitoring for NB recurrence, as >95% of relapses are metastatic, and bone and bone marrow are the most common metastatic sites. MIBG scintigraphy is an accurate method for detecting osteomedullary metastases (Figure 1) as there is no physiological uptake of MIBG in bone or bone marrow. MIBG, an analog of norepinephrine and a guanethidine derivative, is taken up and stored in NB cells expressing the norepinephrine transporter and is radio-iodinated for imaging use (Boubaker & Bischof Delaloye, 2008). MIBG scan has a reported sensitivity and specificity of 88% and 83%, respectively (Vik et al., 2009). In comparison, ^{99m}Tc-technetium bone scan is reported to have a sensitivity of 75% and specificity of 50% for the detection of skeletal metastases (Jacobs et al., 1990). As a result, ^{123}I-MIBG imaging has superseded the use of bone scan for demonstrating bone metastases, with the exception of tumors that are not MIBG-avid (Brisse et al., 2011). Approximately 10% of NB tumors do not concentrate MIBG (Carlin et al., 2003). False-negative MIBG scan has been observed when only a small amount of tumor cells are present in the bone marrow (Kushner et al., 2003b). Hence, bilateral bone marrow biopsy is still recommended in order to exclude bone marrow metastases (Matthay et al., 2010). Small hepatic lesions may not be detected by MIBG due to the high physiological uptake in the liver and are better depicted by ultrasound, CT or MRI (Brisse et al., 2011).

[18]Fluorine-deoxyglucose (FDG) PET scan, which measures the metabolic characteristics of cells, has also been used for detecting NB. Compared with MIBG, FDG-PET was reported to be superior in the evaluation of small soft tissue lesions and Stage 1 and 2 tumors. However, FDG-PET was found to be less sensitive than MIBG in high-risk disease as MIBG was more sensitive than FDG-PET in the detection of bone metastases (Sharp et al., 2009; Taggart et al., 2009). FDG-PET is also limited by the high physiologic uptake of FDG in the brain and can hide skull lesions. Nonetheless, FDG-PET may have a role in monitoring MIBG-negative disease.
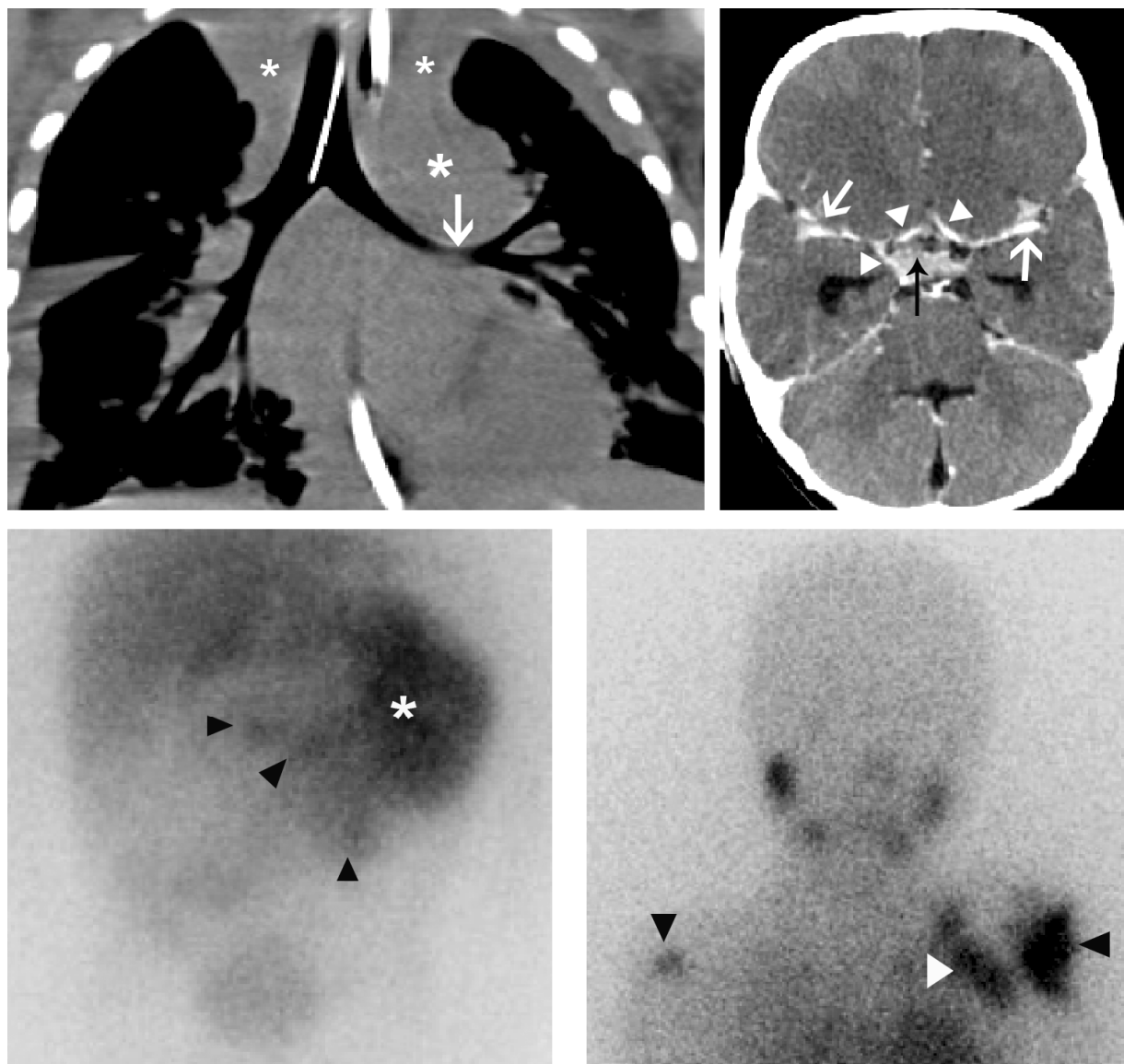
Top left: CT chest shows widespread mediastinal and hilar lymphadenopathy (asterisks) with compression of the left main bronchus (arrow) from distant metastases of recurrent abdominal NB. Patients presented with shortness of breath. Top right: CT brain shows multiple nodular enhancing leptomeningeal deposits in the suprasellar cistern (black arrow) with encasement of the Circle of Willis (Δ) and middle cerebral arteries bilaterally (white arrows) in a NB patient, who presented with increasing drowsiness at the time of isolated CNS relapse. Bottom left: MIBG scan demonstrates a large local recurrence (asterisk) in the left abdomen, with mixed areas of low and intense MIBG uptake. There are also multiple small foci of mild to moderate MIBG uptake in the mesentery and para-aortic locations (▲). Bottom right: MIBG scan shows skeletal metastases in both proximal humeri (▲) and spread to the left axillary lymph nodes (Δ).

Fig. 1. Imaging of NB disease recurrence.

NB patients with symptoms and signs suggestive of CNS metastases are best imaged with CT and/or MRI of the brain and spinal cord for parenchymal brain lesions and leptomeningeal spread (Figure 1). While MIBG can be positive with CNS involvement, the sensitivity of MIBG for CNS metastases is low. Matthay et al. reported that MIBG scans were negative in half of the patients with CNS recurrences (Matthay et al., 2003a). Difficulty in

distinguishing cerebral lesions from skull lesions, especially without the help of SPECT images to localize a lesion, and the presence of meningeal disease without bulky lesions make MIBG unsuitable for evaluating CNS metastases.

3.4 Surveillance of asymptomatic relapse

The risk of relapse, the sensitivity and specificity of a specific investigation for detecting relapse, dose of radiation of an imaging study, invasiveness of a test, need of general anesthesia, and the cost of a study are all important factors to be considered when determining a surveillance protocol to detect asymptomatic relapse. For patients with high-risk NB, early detection of recurrence will likely result in better response to salvage therapy than in the setting of bulky metastatic disease. However, it is unclear whether early detection of recurrence prior to the onset of symptoms will lead to increased cure and whether a specific subgroup of NB patients will benefit from surveillance regimens that identify early relapse.

3.4.1 Surveillance of low and intermediate-risk NB

Patients with low probability of relapse should be followed up with tests that are non-invasive, require minimal or no sedation, and involve no or the lowest doses of radiation. Since children are known to have the highest inherent sensitivity to the carcinogenic effects of ionizing radiation (Brody et al., 2007), patients with low- and intermediate-risk NB who have no prior exposure to radiotherapy should be monitored with ultrasound and ^{123}I-MIBG. The radiation dose of ^{123}I-MIBG is 10% of that of ^{131}I-MIBG (Bombardieri et al., 2003). The INRG Task Force recommends post-therapy surveillance MIBG scan at 6-month intervals for 1 year for low-risk Stage 2 patients, and for 2 years for intermediate-risk patients (Matthay et al., 2010). While the measurement of urine catecholamines is a non-invasive test, it is not used as a follow-up investigation due to its poor sensitivity in detecting relapse. The sensitivity of urine catecholamines is only 23% for detecting isolated local recurrence (Simon et al., 2003).

3.4.2 Surveillance of high-risk NB

High-risk NB patients have a significantly higher risk of relapse with a 2-year EFS survival of 46% (Matthay et al., 2009b). Most patients undergo surveillance studies every 3 months until 3 years from diagnosis. CT, MIBG, and bone marrow examination are the most frequently utilized to monitor for disease recurrence. After this critical period, the frequency and type of follow-up studies are generally tailored to the likelihood of relapse of individual patients.

In a recent study of 91 high-risk patients with asymptomatic relapse, ^{123}I-MIBG scan was reported to have the highest sensitivity (82%) of detecting unsuspected relapse, compared with bone scan, bone marrow examination, CT (head), CT (chest/abdomen/pelvis), and urine catecholamines, with sensitivities of 27%, 28%, 22%, 29%, and 18%, respectively (Kushner et al., 2009). ^{123}I-MIBG scan was the sole indicator of unsuspected relapse in 27% of patients, whereas CT chest/abdomen/pelvis was the only positive test in 6% of patients, CT head in 3% of patients, bone marrow histology in 4.5% of patients, bone scan in 3% of patients, and urine catecholamines in none of the patients. However, ^{123}I-MIBG scan failed to reveal unsuspected relapse in the bone marrow in 25% of patients, in extracranial soft tissue in 21% of patients, and in head/orbits in 13% of patients. This study confirms the limitations of MIBG to detect low levels of bone marrow infiltration, small liver lesions, and

CNS metastases. In addition, urine catecholamine levels have limited use in diagnosing early recurrence with small tumor burden.

3.4.3 Surveillance of minimal residual disease

Minimal residual disease (MRD) in NB refers to the small number of circulating tumor cells present in the bone marrow, peripheral blood, or peripheral blood stem cells. Although histological examination of bone marrow is considered the gold standard for assessing bone marrow metastases, this conventional tool has a detection level of only 1% tumor cells (N.K. Cheung et al., 1997) and does not have sufficient sensitivity to detect MRD. Significant effort has therefore been directed towards the development of MRD detection methods in the last two decades. The ability to measure occult tumor cells is important for increasing the sensitivity of detecting metastases at diagnosis, evaluating response during treatment, and detecting early relapse post therapy.

The three main MRD detection techniques are immunocytology (IC), quantitative reverse transcriptase polymerase chain reaction (QRT-PCR), and flow cytometry (FC) (Beiske et al., 2005). For IC, both the SIOPEN Bone Marrow Committee and the INRG Task Force have recommended disialoganglioside (G_{D2}) as a target cell surface antigen and have developed standardized protocol for IC (Beiske et al., 2009; Swerts et al., 2005). Similarly, standard operating procedures have been developed by the SIOPEN Research Network and INRG Task Force for QRT-PCR, using tyrosine hydroxylase as target mRNA (Beiske et al., 2009; Viprey et al., 2007). The use of multiple molecular markers in QRT-PCR to increase the sensitivity and specificity of MRD detection has also been investigated (I.Y. Cheung et al., 1998; I.Y. Cheung et al., 2008; Stutterheim et al., 2009). FC has the advantage of measuring several antigens on single cells and can screen a large number of cells in a short time. CD9, CD56, CD45, CD81, anti-G_{D2} are the commonly used markers (Beiske et al., 2005). However, FC is considered to be less sensitive than IC for MRD detection in NB.

Despite all the technological advances made in MRD detection, the clinical relevance of MRD remains unclear. While the majority of studies demonstrated the prognostic value of MRD in bone marrow and blood, the level of clinically significant MRD and the timing of MRD were not consistent in these studies (Burchill et al., 2001; Cai et al., 2007; I.Y. Cheung et al., 2003; Moss et al., 1991; Seeger et al., 2000; Stutterheim et al., 2011). The clinical utility of MRD in NB at various stages of therapy requires validation in large prospective multi-center clinical trials using standardized protocols. Which marker(s) should be exploited? What level of MRD is indicative of relapse? Does very early intervention based on MRD improve survival post relapse? Answers to these questions will no doubt influence future surveillance program to monitor early relapse.

4. Survival following disease recurrence

Long-term cure after NB relapse is considered rare. For patients treated in the 1990's, the 5-year post-recurrence survival is 11% (Santana et al., 2008) and the median survival is 8 months (Lau et al., 2004). Patients who relapse within 12 to 16 months from diagnosis did even worse and median survival was only 2.5 months (Lau et al., 2004; Santana et al., 2008). Prognostic factors at diagnosis continue to have a significant impact on survival post relapse (London & Castel et al., 2011). In addition, a small number of patients are reported to have a protracted clinical course after relapse. Chronic NB may become more apparent in the next decade when prolonged survival with multiple recurrences is encountered with increasing frequency with novel therapeutics.

4.1 Factors predictive of survival after relapse

Many of the factors at diagnosis that are prognostic of EFS and overall survival (OS) also influence OS after disease progression or relapse. As stated above, the COG uses age (<18 months, ≥18 months), INSS stage, *MYCN* status, histopathology, and ploidy to assign patients to the appropriate level of treatment intensity at the time of diagnosis. In an INRG analysis of 2,266 patients who experienced first progression/relapse, the median time to relapse was 13 months, and 5-year OS from the time of first relapse was 20% (London & Castel et al., 2011). After disease progression or relapse, factors identified as most highly prognostic of poor OS were age ≥18 months, use of intensive multi-modality treatment at diagnosis, stage 4, elevated serum ferritin, elevated LDH, unfavorable histology, high MKI, and *MYCN* amplification, whereby the presence of any one of these adverse features doubled the risk for death post-relapse. Furthermore, time from diagnosis to first relapse/progression had a significant impact on survival after relapse. However, time-to-first-relapse (TTFR) was associated with OS time in a complex non-linear relationship; patients with TTFR of 36 months or longer had the lowest risk of death, followed by patients who relapsed in the period of 0 to less than 6 months or 18 to 36 months. Patients who relapsed between 6 and 18 months after diagnosis had the highest risk of death. TTFR, older age, higher INSS stage, and *MYCN* amplification were independently prognostic of worse post relapse OS in multivariable analysis. Within the subgroup of patients with *MYCN* amplified tumors and stage 3 and 4 disease, TTFR was the most highly predictive of OS post relapse (London & Castel et al., 2011).

In a retrospective study describing 781 children with NB experiencing tumor recurrence, the 10-year OS was 6.8% after progression and 14.4% after relapse (Garaventa et al., 2009). Similar to the findings of London & Castel et al. (2011), the factors worsening outcome in univariate analysis were age >18 months, advanced stage, high LDH, *MYCN* amplification, and abdominal primary (no multivariable analysis). Most relapses occurred early (median 7.8 months), but 86 (24%) occurred late (median 28 months). Early relapses had a more rapid, unfavorable course, with ~80% of deaths occurring within 2 years, whereas survival time was longer for late relapses. From the German protocols NB90, NB97, and NB2004 (451 high-risk patients), Simon et al. presented data on 232 patients with NB who relapsed after autologous stem cell transplantation (ASCT) as part of initial treatment (Simon et al., 2011). *MYCN* amplification, early recurrence within 18 or 24 months after diagnosis, as well as bone marrow and lung/pleura metastasis at relapse were independently predictive of poor survival in multivariate analysis. Of the patients who received second-line chemotherapy, the 23 patients who underwent a second ASCT had better outcome than the 135 patients who did not have a second ASCT (3 year OS of 43.5% vs. 9.6%).

Two previous single-institution studies in NB also showed that shorter time to first relapse was a significant adverse factor for survival. Lau et al. reviewed 31 patients with NB with relapsed disease and found that patients who relapsed less than 12 months from diagnosis, patients who did not receive salvage therapy, and patients with tumor *MYCN* amplification had significantly shorter survival time (Lau et al., 2004). Santana et al. addressed the study of disease-control intervals in 91 high-risk patients with NB (Santana et al., 2008). The estimated median times to disease recurrence were 18.3, 8.7, and 3.8 months for the first, second, and third recurrences, respectively. Patients with longer initial disease control had a significant post-recurrence survival advantage. This study emphasized the importance of knowing the intervals of disease progression as end points for the design of protocols with new agents.

Ultimately, understanding the genetic differences in early versus late relapsing patients will facilitate selection of appropriate targeted therapy. Meanwhile, it is appropriate to perform

stratification of relapsed patients according to the timing of first relapse, as well as stage, age, and *MYCN* status; this is critical in certain types of study designs, such as randomized phase II trials, to maintain a balance of less favorable patients between treatment arms.

4.2 Outcome of CNS recurrence

If patients recur with neuraxis involvement, the outcome has always been considered ominous, either with or without treatment. The median survival from CNS recurrence ranged from 2 to 14 months and survival beyond 18 months was very rare (Kellie et al., 1991; Kramer et al., 2001; Matthay et al., 2003a; Shaw & Eden, 1992). It was also suggested that patients with meningeal recurrence had the shortest survival (0.9 months) (Matthay et al., 2003a). However, CNS-directed radioimmunotherapy may improve the outcome of these patients (Croog et al., 2010; Kramer et al., 2010) (refer to Section 5.2 for details).

4.3 Chronic neuroblastoma and late relapse

Chronic or indolent NB generally refers to active NB beyond four to five years from diagnosis. This can arise from persistent stable disease, first recurrence followed by a protracted disease course with multiple recurrences or from late relapse with or without prolonged survival.

4.3.1 Chronic neuroblastoma in adolescents and adults

Indolent NB is a more common phenomenon in adolescents and adults than in children, but the actual number of adolescents and adults with NB is very small, since over 90% of NB patients are diagnosed before the of age 10 years. Despite an indolent course and the absence of *MYCN* amplification, the outcome of these patients is very poor. Of the 1,950 NB patients registered with the Children's Cancer Group from 1973 to 1993, 2% of patients were aged between 13 and 18 years, and survival was 7% at 5 years compared with 30% survival in patients aged 1 to 13 years (Franks et al., 1997). Only one tumor from the older age group had *MYCN* amplification. In a report of 1116 children and 53 adolescence (age 10 -18 years), adolescence were also found to have worse outcome than children (10-year OS 20% vs. 39%) and had an indolent course post-recurrence (Conte et al., 2006). Franks et al. described 15 of the 16 NB patients aged between 13 and 33 years subsequently relapsed and 13 died. The median OS was 3.5 years, which is significantly longer than the post-relapse median survival of eight months in children. Moreover, in adolescents and adults, non-Stage 4 patients have an even more protracted course following relapse than Stage 4 patients (median survival 7.8 vs. 2.8 years).

4.3.2 Chronic neuroblastoma in children

Childhood NB may follow a chronic course and has partly been attributed to improved salvage regimens that have become available in the last decade. Children with chronic NB can be separated according to the timing of relapse. In a study by Kushner et al. describing NB patients who were younger than 10 years old at diagnosis and had metastatic disease five years or more from diagnosis, 21 Stage 4 patients had first relapse <4 years from diagnosis (Kushner et al., 2002). All 21 patients had a second recurrence and 13 had a third recurrence. Seventeen (81%) died of NB between 5 and 9.8 years from diagnosis, and four were alive with disease 5.6 to 7.8 years from diagnosis. The study also included Stage 4 patients who presented with late first relapse (4.3 to 13 years from diagnosis). This group of late relapse patients appears to have an even more chronic course. Three of the nine patients

died of NB at 7.3 to 10.4 years from diagnosis, three were alive with disease 6.7 to 14.1 years, and three were in second remission 6.8 to 19.5 years. Multiple recurrences were also described by Santana et al. (Santana et al., 2008). In a cohort of 66 relapsed NB patients, 12% had one recurrence (median 15.7 months from diagnosis), 21% had two recurrences (median 7.2 months from last relapse), and 67% had at least three recurrences (median 3.5 months). The interval between each successive recurrence decreased.

4.3.3 Late relapse

First relapse occurring more than five years from initial diagnosis is uncommon and is observed in 3% of NB patients who remain in remission for the first five years. In a study where 406 remission patients were followed up >5 years from diagnosis, 18 patients relapsed and 14 of these were late first recurrences (Cotterill et al., 2001). Only two patients were alive at the time of report. A literature review described 30 cases of late NB recurrences (published between 1950 and 1990) (Cervera et al., 1990). In 29 patients, relapse occurred between 5 and 16 years from diagnosis. The outcome was only known in 24 patients, of whom 17 died of NB at 6.5 to 24.7 years from diagnosis. One case was exceptional in that a man, who was 29 years old at diagnosis, relapsed 52 years later (Mir et al., 1987). Kushner et al. also reported a man, who relapsed 38 years after he was diagnosed at age 8 years (Kushner et al., 2002).

5. Therapeutic strategies for relapsed NB

Extensive effort has been put into the development of drugs to treat high-risk NB. The most recent advance is the use of anti-G_{D2} immunotherapy to eradicate MRD (Yu et al., 2010). However, at this point of time, 50% of high-risk NB patients will relapse after receiving conventional treatment without immunotherapy. Current salvage regimens can induce response or arrest disease progression in 60% of relapsed patients (Lau et al., 2004), but to date no salvage treatment regimens are known to be curative. A number of novel agents with anti-NB activities are currently under investigation and are mostly available to relapsed patients who are eligible for specific phase I/II clinical trials.

5.1 Conventional chemotherapeutics

Intensive regimens using conventional chemotherapeutic agents were used in relapsed NB patients in the 1990's, and they include various combinations of high doses of carboplatin, cisplatin, cyclophosphamide, ifosfamide, doxorubicin, and etoposide (Alvarado et al., 1997; Campbell et al., 1993; Kreissman et al., 1997). Although these treatments achieved responses in 35 to 50% of patients, they were accompanied by unacceptably high toxicities with no improvement in long-term outcome and are rarely indicated in current settings. Myeloablative therapy is also rarely indicated for the same reason, with the exception of metastatic relapse in patients with low and intermediate-risk NB, who may be salvaged with frontline myeloablative regimen used for high-risk disease. However, the use of moderate dose of conventional chemotherapy in combination with new agents is an important means of assessing new agents in phase I/II studies.

5.2 Palliative radiotherapy

While radiotherapy (RT) cannot cure relapse, it provides rapid and effective symptom control and palliation for skeletal, soft tissue, and CNS metastases. NB often remains radiosensitive at relapse. Palliative RT is given for bone pain, obstructive symptoms from

soft tissue mass and neurological symptoms from CNS disease. 200 to 300cGy is delivered for each fraction and the number of fractions given depends on response (Caussa et al., 2011; Paulino, 2003). The median total RT dose is around 2000cGy. RT can achieve a response rate of 63 to 79% in skeletal metastases, 67 to 84% in soft tissue sites, and 44 to 80% in CNS metastases (Caussa et al., 2011; Halperin & Cox, 1986; Paulino, 2003).

5.3 Second-line chemotherapy

Further dose intensification with conventional chemotherapeutics is not a practical option with disease recurrence. Second line chemotherapies with mild to modest toxicities that have not been included in frontline treatment are often considered for salvage. Topotecan, irinotecan, temozolomide are commercially available drugs. Other agents such as fenretinide and vorinostat are still undergoing clinical trials for NB treatment.

5.3.1 Topoisomerase I inhibitors

Over the past decade, topotecan and irinotecan, both topoisomerase I inhibitors with proven anti-NB activity, have been frequently used in relapsed NB. Targeting the DNA-relaxing enzyme topoisomerase I results in failure of DNA re-ligation during DNA replication and repair. In a phase II trial, partial responses (PR) or better were observed in 32% of the 57 relapsed patients receiving topotecan and cyclophosphamide and in 19% of the 62 patients in the topotecan alone group. While the topotecan/cyclophosphamide group had a significantly better 3-year PFS (10% vs. 0%), there was no difference in 3-year OS (17% vs. 14%) (London et al., 2010). The combination of topotecan and cyclophosphamide has been the most extensively utilized salvage regimen, and 60% of relapsed patients are expected to experience grade 3 or 4 hematological toxicity. Vincristine or etoposide have also been added as a third drug to topotecan/cyclophosphamide, and PR or better were obtained in 52% and 61% of relapsed patients, respectively (Kushner et al., 2010; Simon et al., 2007).

In many cases, irinotecan is combined with temozolomide. A phase II study of irinotecan/ oral temozolomide demonstrated a response rate of 19% and stable disease (SD) of 56% in relapsed patients (Bagatell et al., 2011). Diarrhoea is a common side effect of irinotecan, and Grade 3 or 4 diarrhoea was reported in 6% of patients. Oral irinotecan/temozolomide, which has the benefit of home administration and reduced costs, has also been tested, with 50% of patients achieving response or stable disease (Wagner et al., 2009). High dose carboplatin/irinotecan/temozolomide had a response rate of 68% (Kushner et al., 2011).

5.3.2 Fenretinide

Fenretinide (N-4-hydroxyphenyl retinamide, [4-HPR]) is a synthetic retinoid with cytotoxic and growth inhibitory effects on NB cell lines. Unlike 13-cis- and all-trans-retinoic acids, fenretinide does not induce cellular differentiation, but induces apoptosis (Di Vinci et al., 1994). The mechanisms of action include de novo ceramide synthesis, generation of reactive oxygen species (Maurer et al., 1999), anti-angiogenesis (Ribatti et al., 2003), and increased natural-killer cell activity (Villa et al., 1993). Phase I trials of oral fenretinide in relapsed NB patients demonstrated SD in 43% to 77% of patients (Garaventa et al., 2003; Villablanca et al., 2006). One NB patient had a complete response (CR). However, capsule formulation of fenretinide has poor bioavailability and wide interpatient variation, and the large capsules present a major challenge for children to ingest. LYM-X-SORB, a novel organized lipid matrix, can increase the oral bioavailability of fenretinide (Maurer et al., 2007). A phase I study of fenretinide/LYM-X-SORB oral powder formulation in NB patients is underway.

5.3.3 Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, [SAHA]) is an oral histone deacetylase (HDAC) inhibitor. HDAC inhibition leads to histone acetylation, opening of chromatin structure, and reactivation of previously silenced genes (Johnstone, 2002). In NB, HDAC inhibitors have been shown to induce apoptosis and impair VEGF production (Muhlethaler-Mottet et al., 2008), restore the p53 pathway (Condorelli et al., 2008), synergize with retinoic acid to inhibit growth (Coffey et al., 2001), and enhance RT (S. Mueller et al., 2011). In a phase I trial of vorinostat, one CR was observed in a NB patient receiving vorinostat in combination with 13-cis-retinoic acid (Fouladi et al., 2010).

5.4 Immunotherapy

G_{D2}, disialoganglioside, is the most common tumor-associated antigen targeted in NB immunotherapy. G_{D2} is an ideal target as it is a ubiquitous and abundant surface glycolipid that is present on NB cells but in normal tissue except for neurons. The three main anti-G_{D2} monoclonal antibodies (MoAb) are 3F8, ch14.18, and hu14.18-IL-2. Tumor cells are killed via complement activation and antibody-dependent cell-mediated cytotoxicity (ADCC) that can be augmented by cytokines, e.g. interleukin-2 (IL-2) and GM-CSF (Hank et al., 1990; Imai et al., 2005; B.M. Mueller et al., 1990). Chimeric antibody Ch14.18/IL-2/GM-CSF immunotherapy is effective against MRD in the post-consolidation setting, as shown in a recent phase III randomized trial in primary NB (Yu et al., 2010). In recurrent NB, unsustained response to immunotherapy is restricted to non-bulky disease in the bone marrow and small MIBG-avid lesions. Common side effects include pain, capillary leak syndrome, hypotension, and allergic reaction.

3F8 is a murine MoAb and is the first MoAb to be studied in NB patients (N.K. Cheung et al., 1987). In a phase II study of 3F8/GMCSF, CR in five of 10 patients was restricted to the bone marrow and all developed progressive disease at other sites (Kushner et al., 2001). Similar results were seen in a phase II study of humanized 14.18-IL-2, a fusion protein of humanized 14.18 anti-G_{D2} MoAb linked to IL-2 (Shusterman et al., 2010). Of the 20 patients with small disease burden, CR was achieved in five patients, three of whom had bone marrow disease only by histology at relapse, one had a single MIBG-avid lesion, and one had both bone marrow and bone disease.

Unlike high-risk patients, patients who have locoregional NB and relapse with metastatic disease may be salvaged with immunotherapy. Kushner et al. reported three of five patients, who were initially treated with surgery alone for low-risk NB and subsequently relapsed with metastatic disease, were in CR at four to seven years (Kushner et al., 2003a). These patients received an intensive salvage regimen containing intensive chemotherapy, 3F8 MoAb, [131]I-3F8, local RT, and 13-cis-retinoic acid.

5.5 Radionuclide therapy

MIBG is taken up by 90% of NB tumors. MIBG labeled with therapeutic isotope ^{131}I is used to deliver target specific RT in NB for >20 years. ^{131}I-MIBG therapy is generally well tolerated, except for myelosuppression that may require stem cell support in heavily pretreated patients (DuBois et al., 2004). MIBG monotherapy achieved responses in up to a third of relapsed patients at doses ≥12 mCi/kg, but with no long-term cure (DuBois & Matthay, 2008). In a large phase II trial of 164 patients receiving 12 to 18 mCi/kg of ^{131}I-MIBG, the overall response rate was 36% and SD rate was 36%, and the 2-year OS was 29% (Matthay et al., 2007). The additional benefits of dose intensification with tandem ^{131}I-MIBG

infusions (Matthay et al., 2009a) and of including ^{131}I-MIBG with myeloablative therapy requires further studies (Matthay et al., 2006).

^{131}I-MIBG therapy may be enhanced with radiosensitizers such as cisplatin (Mastrangelo et al., 1997) and topotecan (Gaze et al., 2005) or with non-carrier added radiolabeled MIBG. Conventional preparation of ^{131}I-MIBG has large quantities of unlabeled or cold (non-radioactive) MIBG in the final formulation. Saturation of the norepinephrine transporter by unlabeled MIBG reduces the efficacy while increasing the side-effects. This can be circumvented by using the Ultratrace solid-phase preparation technique to synthesize non-carrier added radiolabeled MIBG (Ultratrace ^{131}I-MIBG). This novel formulation resulted in greater tumor uptake and efficacy in NB xenografts (Barrett et al., 2010). The increased uptake and retention of Ultratrace ^{131}I-MIBG may have therapeutic benefit by allowing further intensification of MIBG therapy.

5.6 Targeted therapies

Targeted therapies with potential anti-NB activities include small molecule inhibitors against ALK (anaplastic lymphoma kinase), aurora A kinase, trk tyrosine kinase, Akt/PI3-kinase, and EGFR, and monoclonal antibodies against VEGF, IGF-1, and TRAIL receptor.

5.6.1 ALK inhibition

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase and was identified as a NB predisposition gene (Mosse et al., 2008). *ALK* somatic mutations and amplification are found in 8% of primary NB. Of interest, a subset of tumors expressing high mRNA levels of wild-type *ALK* have similar genotype and poor clinical outcome to tumors with *ALK* mutations/amplification (Schulte et al., 2011). Preclinical data show that ALK inhibition diminishes growth in cells with *ALK* mutations, as well as in cells overexpressing wild-type *ALK* (Janoueix-Lerosey et al., 2008). Hence, ALK inhibitors may potentially be effective in NB tumors expressing high levels of ALK. A phase I/II trial of a small molecule inhibitor of ALK is in progress.

5.6.2 Anti-angiogenesis

NB is a highly vascular tumor and tumor angiogenesis is associated with metastatic disease and poor outcome (Meitar et al., 1996). Bevacizumab (MoAb against vascular endothelial growth factor (VEGF)), did not lead to any objective responses when used as a single agent in children with refractory solid tumors (Glade Bender et al., 2008). The efficacy of bevacizumab in combination with irinotecan/temozolomide and with the radiolabeled ^{131}I-3F8 antibody in relapsed NB is currently being investigated.

5.6.3 TRK inhibition

TrkB, a member of the Trk (NTRK) neurotrophin tyrosine kinase receptors, is highly expressed in unfavorable NB (Brodeur et al., 2009; Nakagawara et al., 1994). TrkB overexpression results in increased chemoresistance in NB cells (Ho et al., 2002). Lestaurtinib (CEP-701), a selective Trk tyrosine kinase inhibitor, has anti-tumor activity in NB xenograft models, both as a single agent and in combination with topotecan/cyclophosphamide and with irinotecan/temozolomide (Iyer et al., 2010). In a phase I trial of lestaurtinib, two PR and nine SD were reported in 46 patients with refractory NB (Minturn et al., 2011).

5.7 Treatment of CNS relapse

The outcome of CNS recurrence is dismal with conventional chemotherapeutic agents. The use of CNS-directed radioimmunotherapy (RIT) may improve the prognosis of this group of patients. RIT enables the targeted delivery of RT to tumor cells (Kramer et al., 2007). In a retrospective analysis of 14 patients who received craniospinal irradiation together with irinotecan as a radiosensitizer, followed by intra-Ommaya (IO) RIT (^{131}I-8H9 or ^{131}I-3F8), 10 were alive with no CNS disease at 15.2 to 62.7 months from CNS relapse, three were alive with disease at 24.6 to 30.2 months, and one died from other cause but without disease at 21.9 months (Croog et al., 2010). This is in contrast with the 12 patients, who only received whole/partial brain or partial spine radiotherapy and all succumbed 4.2 to 23.9 months later. In addition, the same group treated 21 patients with CNS recurrences with an intensive regimen containing IO RIT (^{131}I-8H9 or ^{131}I-3F8) with promising results (Kramer et al., 2010). Seventeen patients were alive without CNS disease at 7 to 74 months post CNS relapse. In addition to IO RIT, patients also received CSI with irinotecan, irinotecan/temozolomide/carboplatin, systemic immunotherapy (anti-3F8 with GMCSF), and maintenance treatment with 13-cis-retinoic acid and oral temozolomide. The long-term treatment consequences of CNS directed RIT are yet to be evaluated.

The use of IO topotecan has also been described in a NB case report of isolated CNS metastases. This patient, who received both IO and IV topotecan, had a CR of both parenchymal and leptomeningeal disease and was progression-free for 18 weeks (Sirachainan et al., 2008).

6. Conclusion

Although long-term disease-free survival after recurrent NB remains extremely poor, salvage regimens in the recent era have altered the natural disease course and prolong post-relapse survival, with a small subset of chronic patients experiencing multiple recurrences or non-remitting disease. However, it is difficult to predict response to salvage therapy and survival time post relapse. Knowledge in this area is limited. Which patients should be offered multi-modality treatment and which patients should receive oral agents with minimal toxicity? How can we ensure quality of life is not jeopardized by unrealistic expectations? These are difficult questions clinicians must face whenever a child with NB relapses.

Furthermore, surveillance for disease recurrence can cause significant emotional and financial burden. Can detection of early asymptomatic relapse improve quality of life or change long-term survival? Can the detection of early molecular relapse by monitoring MRD improve response to salvage therapy and increase survival? What is a clinical significant MRD level? Further research is needed to provide answers to these questions to facilitate development of effective surveillance protocols.

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8. References

Alvarado, C.S., Kretschmar, C., Joshi, V.V., Toledano, S., Cantor, A., Strother, D., Nitschke, R. & Castleberry, R.P. (1997). Chemotherapy for patients with recurrent or refractory neuroblastoma: a POG Phase II study. *J Pediatr Hematol Oncol*, Vol.19, No.1, pp. 62-67.

Ambros, P.F., Ambros, I.M., Brodeur, G.M., Haber, M., Khan, J., Nakagawara, A., Schleiermacher, G., Speleman, F., Spitz, R., London, W.B., Cohn, S.L., Pearson, A.D. & Maris, J.M. (2009). International consensus for neuroblastoma molecular diagnostics: report from the International Neuroblastoma Risk Group (INRG) Biology Committee. *Br J Cancer*, Vol.100, No.9, pp. 1471-1482.

Bagatell, R., London, W.B., Wagner, L.M., Voss, S.D., Stewart, C.F., Maris, J.M., Kretschmar, C. & Cohn, S.L. (2011). Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: a Children's Oncology Group study. *J Clin Oncol*, Vol.29, No.2, pp. 208-213.

Barrett, J.A., Joyal, J.L., Hillier, S.M., Maresca, K.P., Femia, F.J., Kronauge, J.F., Boyd, M., Mairs, R.J. & Babich, J.W. (2010). Comparison of high-specific-activity ultratrace 123/131I-MIBG and carrier-added 123/131I-MIBG on efficacy, pharmacokinetics, and tissue distribution. *Cancer Biother Radiopharm*, Vol.25, No.3, pp. 299-308.

Beiske, K., Ambros, P.F., Burchill, S.A., Cheung, I.Y. & Swerts, K. (2005). Detecting minimal residual disease in neuroblastoma patients-the present state of the art. *Cancer Lett*, Vol.228, No.1-2, pp. 229-240.

Beiske, K., Burchill, S.A., Cheung, I.Y., Hiyama, E., Seeger, R.C., Cohn, S.L., Pearson, A.D. & Matthay, K.K. (2009). Consensus criteria for sensitive detection of minimal neuroblastoma cells in bone marrow, blood and stem cell preparations by immunocytology and QRT-PCR: recommendations by the International Neuroblastoma Risk Group Task Force. *Br J Cancer*, Vol.100, No.10, pp. 1627-1637.

Bombardieri, E., Aktolun, C., Baum, R.P., Bishof-Delaloye, A., Buscombe, J., Chatal, J.F., Maffioli, L., Moncayo, R., Mortelmans, L. & Reske, S.N. (2003). 131I/123I-metaiodobenzylguanidine (MIBG) scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging*, Vol.30, No.12, pp. BP132-139.

Boubaker, A. & Bischof Delaloye, A. (2008). MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. *Q J Nucl Med Mol Imaging*, Vol.52, No.4, pp. 388-402.

Brisse, H.J., McCarville, M.B., Granata, C., Krug, K.B., Wootton-Gorges, S.L., Kanegawa, K., Giammarile, F., Schmidt, M., Shulkin, B.L., Matthay, K.K., Lewington, V.J., Sarnacki, S., Hero, B., Kaneko, M., London, W.B., Pearson, A.D., Cohn, S.L. & Monclair, T. (2011). Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project. *Radiology*.

Brodeur, G.M., Minturn, J.E., Ho, R., Simpson, A.M., Iyer, R., Varela, C.R., Light, J.E., Kolla, V. & Evans, A.E. (2009). Trk receptor expression and inhibition in neuroblastomas. *Clin Cancer Res*, Vol.15, No.10, pp. 3244-3250.

Brody, A.S., Frush, D.P., Huda, W. & Brent, R.L. (2007). Radiation risk to children from computed tomography. *Pediatrics*, Vol.120, No.3, pp. 677-682.

Burchill, S.A., Lewis, I.J., Abrams, K.R., Riley, R., Imeson, J., Pearson, A.D., Pinkerton, R. & Selby, P. (2001). Circulating neuroblastoma cells detected by reverse transcriptase polymerase chain reaction for tyrosine hydroxylase mRNA are an independent poor

prognostic indicator in stage 4 neuroblastoma in children over 1 year. *J Clin Oncol*, Vol.19, No.6, pp. 1795-1801.

Cai, J.Y., Tang, Y.J., Jiang, L.M., Pan, C., Chen, J. & Tang, J.Y. (2007). Prognostic influence of minimal residual disease detected by flow cytometry and peripheral blood stem cell transplantation by CD34+ selection in childhood advanced neuroblastoma. *Pediatr Blood Cancer*, Vol.49, No.7, pp. 952-957.

Campbell, L.A., Seeger, R.C., Harris, R.E., Villablanca, J.G. & Matthay, K.K. (1993). Escalating dose of continuous infusion combination chemotherapy for refractory neuroblastoma. *J Clin Oncol*, Vol.11, No.4, pp. 623-629.

Carlin, S., Mairs, R.J., McCluskey, A.G., Tweddle, D.A., Sprigg, A., Estlin, C., Board, J., George, R.E., Ellershaw, C., Pearson, A.D., Lunec, J., Montaldo, P.G., Ponzoni, M., van Eck-Smit, B.L., Hoefnagel, C.A., van den Brug, M.D., Tytgat, G.A. & Caron, H.N. (2003). Development of a real-time polymerase chain reaction assay for prediction of the uptake of meta-[(131)I]iodobenzylguanidine by neuroblastoma tumors. *Clin Cancer Res*, Vol.9, No.9, pp. 3338-3344.

Caussa, L., Hijal, T., Michon, J. & Helfre, S. (2011). Role of palliative radiotherapy in the management of metastatic pediatric neuroblastoma: a retrospective single-institution study. *Int J Radiat Oncol Biol Phys*, Vol.79, No.1, pp. 214-219.

Cervera, A., Kingston, J.E. & Malpas, J.S. (1990). Late recurrence of neuroblastoma: a report of five cases and review of the literature. *Pediatr Hematol Oncol*, Vol.7, No.4, pp. 311-322.

Cheung, I.Y., Barber, D. & Cheung, N.K. (1998). Detection of microscopic neuroblastoma in marrow by histology, immunocytology, and reverse transcription-PCR of multiple molecular markers. *Clin Cancer Res*, Vol.4, No.11, pp. 2801-2805.

Cheung, I.Y., Feng, Y., Gerald, W. & Cheung, N.K. (2008). Exploiting gene expression profiling to identify novel minimal residual disease markers of neuroblastoma. *Clin Cancer Res*, Vol.14, No.21, pp. 7020-7027.

Cheung, I.Y., Lo Piccolo, M.S., Kushner, B.H. & Cheung, N.K. (2003). Early molecular response of marrow disease to biologic therapy is highly prognostic in neuroblastoma. *J Clin Oncol*, Vol.21, No.20, pp. 3853-3858.

Cheung, N.K., Heller, G., Kushner, B.H., Liu, C. & Cheung, I.Y. (1997). Detection of metastatic neuroblastoma in bone marrow: when is routine marrow histology insensitive? *J Clin Oncol*, Vol.15, No.8, pp. 2807-2817.

Cheung, N.K., Lazarus, H., Miraldi, F.D., Abramowsky, C.R., Kallick, S., Saarinen, U.M., Spitzer, T., Strandjord, S.E., Coccia, P.F. & Berger, N.A. (1987). Ganglioside GD2 specific monoclonal antibody 3F8: a phase I study in patients with neuroblastoma and malignant melanoma. *J Clin Oncol*, Vol.5, No.9, pp. 1430-1440.

Coffey, D.C., Kutko, M.C., Glick, R.D., Butler, L.M., Heller, G., Rifkind, R.A., Marks, P.A., Richon, V.M. & La Quaglia, M.P. (2001). The histone deacetylase inhibitor, CBHA, inhibits growth of human neuroblastoma xenografts in vivo, alone and synergistically with all-trans retinoic acid. *Cancer Res*, Vol.61, No.9, pp. 3591-3594.

Cohn, S.L., Pearson, A.D., London, W.B., Monclair, T., Ambros, P.F., Brodeur, G.M., Faldum, A., Hero, B., Iehara, T., Machin, D., Mosseri, V., Simon, T., Garaventa, A., Castel, V. & Matthay, K.K. (2009). The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol*, Vol.27, No.2, pp. 289-297.

Condorelli, F., Gnemmi, I., Vallario, A., Genazzani, A.A. & Canonico, P.L. (2008). Inhibitors of histone deacetylase (HDAC) restore the p53 pathway in neuroblastoma cells. *Br J Pharmacol*, Vol.153, No.4, pp. 657-668.

Conte, M., Parodi, S., De Bernardi, B., Milanaccio, C., Mazzocco, K., Angelini, P., Viscardi, E., Di Cataldo, A., Luksch, R. & Haupt, R. (2006). Neuroblastoma in adolescents: the Italian experience. *Cancer*, Vol.106, No.6, pp. 1409-1417.

Cotterill, S.J., Pearson, A.D., Pritchard, J., Kohler, J.A. & Foot, A.B. (2001). Late relapse and prognosis for neuroblastoma patients surviving 5 years or more: a report from the European Neuroblastoma Study Group "Survey". *Med Pediatr Oncol*, Vol.36, No.1, pp. 235-238.

Croog, V.J., Kramer, K., Cheung, N.K., Kushner, B.H., Modak, S., Souweidane, M.M. & Wolden, S.L. (2010). Whole neuraxis irradiation to address central nervous system relapse in high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys*, Vol.78, No.3, pp. 849-854.

Di Vinci, A., Geido, E., Infusini, E. & Giaretti, W. (1994). Neuroblastoma cell apoptosis induced by the synthetic retinoid N-(4-hydroxyphenyl)retinamide. *Int J Cancer*, Vol.59, No.3, pp. 422-426.

DuBois, S.G. & Matthay, K.K. (2008). Radiolabeled metaiodobenzylguanidine for the treatment of neuroblastoma. *Nucl Med Biol*, Vol.35 Suppl 1, pp. S35-48.

DuBois, S.G., Messina, J., Maris, J.M., Huberty, J., Glidden, D.V., Veatch, J., Charron, M., Hawkins, R. & Matthay, K.K. (2004). Hematologic toxicity of high-dose iodine-131-metaiodobenzylguanidine therapy for advanced neuroblastoma. *J Clin Oncol*, Vol.22, No.12, pp. 2452-2460.

Evans, A.E., D'Angio, G.J. & Randolph, J. (1971). A proposed staging for children with neuroblastoma. Children's cancer study group A. *Cancer*, Vol.27, No.2, pp. 374-378.

Fouladi, M., Park, J.R., Stewart, C.F., Gilbertson, R.J., Schaiquevich, P., Sun, J., Reid, J.M., Ames, M.M., Speights, R., Ingle, A.M., Zwiebel, J., Blaney, S.M. & Adamson, P.C. (2010). Pediatric phase I trial and pharmacokinetic study of vorinostat: a Children's Oncology Group phase I consortium report. *J Clin Oncol*, Vol.28, No.22, pp. 3623-3629.

Franks, L.M., Bollen, A., Seeger, R.C., Stram, D.O. & Matthay, K.K. (1997). Neuroblastoma in adults and adolescents: an indolent course with poor survival. *Cancer*, Vol.79, No.10, pp. 2028-2035.

Garaventa, A., Luksch, R., Lo Piccolo, M.S., Cavadini, E., Montaldo, P.G., Pizzitola, M.R., Boni, L., Ponzoni, M., Decensi, A., De Bernardi, B., Bellani, F.F. & Formelli, F. (2003). Phase I trial and pharmacokinetics of fenretinide in children with neuroblastoma. *Clin Cancer Res*, Vol.9, No.6, pp. 2032-2039.

Garaventa, A., Parodi, S., De Bernardi, B., Dau, D., Manzitti, C., Conte, M., Casale, F., Viscardi, E., Bianchi, M., D'Angelo, P., Zanazzo, G.A., Luksch, R., Favre, C., Tamburini, A. & Haupt, R. (2009). Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. *Eur J Cancer*, Vol.45, No.16, pp. 2835-2842.

Gaze, M.N., Chang, Y.C., Flux, G.D., Mairs, R.J., Saran, F.H. & Meller, S.T. (2005). Feasibility of dosimetry-based high-dose 131I-meta-iodobenzylguanidine with topotecan as a radiosensitizer in children with metastatic neuroblastoma. *Cancer Biother Radiopharm*, Vol.20, No.2, pp. 195-199.

Glade Bender, J.L., Adamson, P.C., Reid, J.M., Xu, L., Baruchel, S., Shaked, Y., Kerbel, R.S., Cooney-Qualter, E.M., Stempak, D., Chen, H.X., Nelson, M.D., Krailo, M.D., Ingle, A.M., Blaney, S.M., Kandel, J.J. & Yamashiro, D.J. (2008). Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: a Children's Oncology Group Study. *J Clin Oncol*, Vol.26, No.3, pp. 399-405.

Halperin, E.C. & Cox, E.B. (1986). Radiation therapy in the management of neuroblastoma: the Duke University Medical Center experience 1967-1984. *Int J Radiat Oncol Biol Phys*, Vol.12, No.10, pp. 1829-1837.

Hank, J.A., Robinson, R.R., Surfus, J., Mueller, B.M., Reisfeld, R.A., Cheung, N.K. & Sondel, P.M. (1990). Augmentation of antibody dependent cell mediated cytotoxicity following in vivo therapy with recombinant interleukin 2. *Cancer Res*, Vol.50, No.17, pp. 5234-5239.

Ho, R., Eggert, A., Hishiki, T., Minturn, J.E., Ikegaki, N., Foster, P., Camoratto, A.M., Evans, A.E. & Brodeur, G.M. (2002). Resistance to chemotherapy mediated by TrkB in neuroblastomas. *Cancer Res*, Vol.62, No.22, pp. 6462-6466.

Imai, M., Landen, C., Ohta, R., Cheung, N.K. & Tomlinson, S. (2005). Complement-mediated mechanisms in anti-GD2 monoclonal antibody therapy of murine metastatic cancer. *Cancer Res*, Vol.65, No.22, pp. 10562-10568.

Iyer, R., Evans, A.E., Qi, X., Ho, R., Minturn, J.E., Zhao, H., Balamuth, N., Maris, J.M. & Brodeur, G.M. (2010). Lestaurtinib enhances the antitumor efficacy of chemotherapy in murine xenograft models of neuroblastoma. *Clin Cancer Res*, Vol.16, No.5, pp. 1478-1485.

Jacobs, A., Delree, M., Desprechins, B., Otten, J., Ferster, A., Jonckheer, M.H., Mertens, J., Ham, H.R. & Piepsz, A. (1990). Consolidating the role of *I-MIBG-scintigraphy in childhood neuroblastoma: five years of clinical experience. *Pediatr Radiol*, Vol.20, No.3, pp. 157-159.

Janoueix-Lerosey, I., Lequin, D., Brugieres, L., Ribeiro, A., de Pontual, L., Combaret, V., Raynal, V., Puisieux, A., Schleiermacher, G., Pierron, G., Valteau-Couanet, D., Frebourg, T., Michon, J., Lyonnet, S., Amiel, J. & Delattre, O. (2008). Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. *Nature*, Vol.455, No.7215, pp. 967-970.

Johnstone, R.W. (2002). Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*, Vol.1, No.4, pp. 287-299.

Kellie, S.J., Hayes, F.A., Bowman, L., Kovnar, E.H., Langston, J., Jenkins, J.J., 3rd, Pao, W.J., Ducos, R. & Green, A.A. (1991). Primary extracranial neuroblastoma with central nervous system metastases characterization by clinicopathologic findings and neuroimaging. *Cancer*, Vol.68, No.9, pp. 1999-2006.

Kramer, K., Humm, J.L., Souweidane, M.M., Zanzonico, P.B., Dunkel, I.J., Gerald, W.L., Khakoo, Y., Yeh, S.D., Yeung, H.W., Finn, R.D., Wolden, S.L., Larson, S.M. & Cheung, N.K. (2007). Phase I study of targeted radioimmunotherapy for leptomeningeal cancers using intra-Ommaya 131-I-3F8. *J Clin Oncol*, Vol.25, No.34, pp. 5465-5470.

Kramer, K., Kushner, B., Heller, G. & Cheung, N.K. (2001). Neuroblastoma metastatic to the central nervous system. The Memorial Sloan-kettering Cancer Center Experience and A Literature Review. *Cancer*, Vol.91, No.8, pp. 1510-1519.

Kramer, K., Kushner, B.H., Modak, S., Pandit-Taskar, N., Smith-Jones, P., Zanzonico, P., Humm, J.L., Xu, H., Wolden, S.L., Souweidane, M.M., Larson, S.M. & Cheung, N.K.

(2010). Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. *J Neurooncol*, Vol.97, No.3, pp. 409-418.

Kreissman, S.G., Rackoff, W., Lee, M. & Breitfeld, P.P. (1997). High dose cyclophosphamide with carboplatin: a tolerable regimen suitable for dose intensification in children with solid tumors. *J Pediatr Hematol Oncol*, Vol.19, No.4, pp. 309-312.

Kushner, B.H., Kramer, K. & Cheung, N.K. (2001). Phase II trial of the anti-G(D2) monoclonal antibody 3F8 and granulocyte-macrophage colony-stimulating factor for neuroblastoma. *J Clin Oncol*, Vol.19, No.22, pp. 4189-4194.

Kushner, B.H., Kramer, K. & Cheung, N.K. (2002). Chronic neuroblastoma. *Cancer*, Vol.95, No.6, pp. 1366-1375.

Kushner, B.H., Kramer, K., LaQuaglia, M.P. & Cheung, N.K. (2003a). Curability of recurrent disseminated disease after surgery alone for local-regional neuroblastoma using intensive chemotherapy and anti-G(D2) immunotherapy. *J Pediatr Hematol Oncol*, Vol.25, No.7, pp. 515-519.

Kushner, B.H., Kramer, K., Modak, S. & Cheung, N.K. (2009). Sensitivity of surveillance studies for detecting asymptomatic and unsuspected relapse of high-risk neuroblastoma. *J Clin Oncol*, Vol.27, No.7, pp. 1041-1046.

Kushner, B.H., Kramer, K., Modak, S. & Cheung, N.K. (2011). High-dose carboplatin-irinotecan-temozolomide: treatment option for neuroblastoma resistant to topotecan. *Pediatr Blood Cancer*, Vol.56, No.3, pp. 403-408.

Kushner, B.H., Kramer, K., Modak, S., Qin, L.X. & Cheung, N.K. (2010). Differential impact of high-dose cyclophosphamide, topotecan, and vincristine in clinical subsets of patients with chemoresistant neuroblastoma. *Cancer*, Vol.116, No.12, pp. 3054-3060.

Kushner, B.H., Yeh, S.D., Kramer, K., Larson, S.M. & Cheung, N.K. (2003b). Impact of metaiodobenzylguanidine scintigraphy on assessing response of high-risk neuroblastoma to dose-intensive induction chemotherapy. *J Clin Oncol*, Vol.21, No.6, pp. 1082-1086.

Lau, L., Tai, D., Weitzman, S., Grant, R., Baruchel, S. & Malkin, D. (2004). Factors influencing survival in children with recurrent neuroblastoma. *J Pediatr Hematol Oncol*, Vol.26, No.4, pp. 227-232.

London, W.B., Castel, V., Monclair, T., Ambros, P.F., Pearson, A.D.J., Cohn, S.L., Berthold, F., Nakagawara, A., Ladenstein, R.L., Iehara, T. & Matthay, K.K. (2011). Clinical and biologic features predictive of survival after relapse of neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) Project. *J Clin Oncol (Jul 18, Epub ahead of print)*.

London, W.B., Castleberry, R.P., Matthay, K.K., Look, A.T., Seeger, R.C., Shimada, H., Thorner, P., Brodeur, G., Maris, J.M., Reynolds, C.P. & Cohn, S.L. (2005). Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol*, Vol.23, No.27, pp. 6459-6465.

London, W.B., Frantz, C.N., Campbell, L.A., Seeger, R.C., Brumback, B.A., Cohn, S.L., Matthay, K.K., Castleberry, R.P. & Diller, L. (2010). Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. *J Clin Oncol*, Vol.28, No.24, pp. 3808-3815.

Mastrangelo, R., Tornesello, A., Lasorella, A., Iavarone, A., Mastrangelo, S., Riccardi, R., Diociaiuti, L., Rufini, V., Pession, A. & Troncone, L. (1997). Optimal use of the 131-I-

metaiodobenzylguanidine and cisplatin combination in advanced neuroblastoma. *J Neurooncol*, Vol.31, No.1-2, pp. 153-158.

Matthay, K.K., Brisse, H., Couanet, D., Couturier, J., Benard, J., Mosseri, V., Edeline, V., Lumbroso, J., Valteau-Couanet, D. & Michon, J. (2003a). Central nervous system metastases in neuroblastoma: radiologic, clinical, and biologic features in 23 patients. *Cancer*, Vol.98, No.1, pp. 155-165.

Matthay, K.K., Edeline, V., Lumbroso, J., Tanguy, M.L., Asselain, B., Zucker, J.M., Valteau-Couanet, D., Hartmann, O. & Michon, J. (2003b). Correlation of early metastatic response by 123I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. *J Clin Oncol*, Vol.21, No.13, pp. 2486-2491.

Matthay, K.K., Quach, A., Huberty, J., Franc, B.L., Hawkins, R.A., Jackson, H., Groshen, S., Shusterman, S., Yanik, G., Veatch, J., Brophy, P., Villablanca, J.G. & Maris, J.M. (2009a). Iodine-131--metaiodobenzylguanidine double infusion with autologous stem-cell rescue for neuroblastoma: a new approaches to neuroblastoma therapy phase I study. *J Clin Oncol*, Vol.27, No.7, pp. 1020-1025.

Matthay, K.K., Reynolds, C.P., Seeger, R.C., Shimada, H., Adkins, E.S., Haas-Kogan, D., Gerbing, R.B., London, W.B. & Villablanca, J.G. (2009b). Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol*, Vol.27, No.7, pp. 1007-1013.

Matthay, K.K., Shulkin, B., Ladenstein, R., Michon, J., Giammarile, F., Lewington, V., Pearson, A.D. & Cohn, S.L. (2010). Criteria for evaluation of disease extent by (123)I-metaiodobenzylguanidine scans in neuroblastoma: a report for the International Neuroblastoma Risk Group (INRG) Task Force. *Br J Cancer*, Vol.102, No.9, pp. 1319-1326.

Matthay, K.K., Tan, J.C., Villablanca, J.G., Yanik, G.A., Veatch, J., Franc, B., Twomey, E., Horn, B., Reynolds, C.P., Groshen, S., Seeger, R.C. & Maris, J.M. (2006). Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study. *J Clin Oncol*, Vol.24, No.3, pp. 500-506.

Matthay, K.K., Yanik, G., Messina, J., Quach, A., Huberty, J., Cheng, S.C., Veatch, J., Goldsby, R., Brophy, P., Kersun, L.S., Hawkins, R.A. & Maris, J.M. (2007). Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *J Clin Oncol*, Vol.25, No.9, pp. 1054-1060.

Maurer, B.J., Kalous, O., Yesair, D.W., Wu, X., Janeba, J., Maldonado, V., Khankaldyyan, V., Frgala, T., Sun, B.C., McKee, R.T., Burgess, S.W., Shaw, W.A. & Reynolds, C.P. (2007). Improved oral delivery of N-(4-hydroxyphenyl)retinamide with a novel LYM-X-SORB organized lipid complex. *Clin Cancer Res*, Vol.13, No.10, pp. 3079-3086.

Maurer, B.J., Metelitsa, L.S., Seeger, R.C., Cabot, M.C. & Reynolds, C.P. (1999). Increase of ceramide and induction of mixed apoptosis/necrosis by N-(4-hydroxyphenyl)-retinamide in neuroblastoma cell lines. *J Natl Cancer Inst*, Vol.91, No.13, pp. 1138-1146.

Meitar, D., Crawford, S.E., Rademaker, A.W. & Cohn, S.L. (1996). Tumor angiogenesis correlates with metastatic disease, N-myc amplification, and poor outcome in human neuroblastoma. *J Clin Oncol*, Vol.14, No.2, pp. 405-414.

Minturn, J.E., Evans, A.E., Villablanca, J.G., Yanik, G.A., Park, J.R., Shusterman, S., Groshen, S., Hellriegel, E.T., Bensen-Kennedy, D., Matthay, K.K., Brodeur, G.M. & Maris, J.M. (2011). Phase I trial of lestaurtinib for children with refractory neuroblastoma: a new approaches to neuroblastoma therapy consortium study. *Cancer Chemother Pharmacol*.

Mir, R., Phillips, S.L., Schwartz, G., Mathur, R., Khan, A. & Kahn, L.B. (1987). Metastatic neuroblastoma after 52 years of dormancy. *Cancer*, Vol.60, No.10, pp. 2510-2514.

Monclair, T., Brodeur, G.M., Ambros, P.F., Brisse, H.J., Cecchetto, G., Holmes, K., Kaneko, M., London, W.B., Matthay, K.K., Nuchtern, J.G., von Schweinitz, D., Simon, T., Cohn, S.L. & Pearson, A.D. (2009). The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *J Clin Oncol*, Vol.27, No.2, pp. 298-303.

Moss, T.J., Reynolds, C.P., Sather, H.N., Romansky, S.G., Hammond, G.D. & Seeger, R.C. (1991). Prognostic value of immunocytologic detection of bone marrow metastases in neuroblastoma. *N Engl J Med*, Vol.324, No.4, pp. 219-226.

Mosse, Y.P., Laudenslager, M., Longo, L., Cole, K.A., Wood, A., Attiyeh, E.F., Laquaglia, M.J., Sennett, R., Lynch, J.E., Perri, P., Laureys, G., Speleman, F., Kim, C., Hou, C., Hakonarson, H., Torkamani, A., Schork, N.J., Brodeur, G.M., Tonini, G.P., Rappaport, E., Devoto, M. & Maris, J.M. (2008). Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature*, Vol.455, No.7215, pp. 930-935.

Mueller, B.M., Romerdahl, C.A., Gillies, S.D. & Reisfeld, R.A. (1990). Enhancement of antibody-dependent cytotoxicity with a chimeric anti-GD2 antibody. *J Immunol*, Vol.144, No.4, pp. 1382-1386.

Mueller, S., Yang, X., Sottero, T.L., Gragg, A., Prasad, G., Polley, M.Y., Weiss, W.A., Matthay, K.K., Davidoff, A.M., DuBois, S.G. & Haas-Kogan, D.A. (2011). Cooperation of the HDAC inhibitor vorinostat and radiation in metastatic neuroblastoma: efficacy and underlying mechanisms. *Cancer Lett*, Vol.306, No.2, pp. 223-229.

Muhlethaler-Mottet, A., Meier, R., Flahaut, M., Bourloud, K.B., Nardou, K., Joseph, J.M. & Gross, N. (2008). Complex molecular mechanisms cooperate to mediate histone deacetylase inhibitors anti-tumour activity in neuroblastoma cells. *Mol Cancer*, Vol.7, pp. 55.

Nakagawara, A., Azar, C.G., Scavarda, N.J. & Brodeur, G.M. (1994). Expression and function of TRK-B and BDNF in human neuroblastomas. *Mol Cell Biol*, Vol.14, No.1, pp. 759-767.

Parodi, F., Passoni, L., Massimo, L., Luksch, R., Gambini, C., Rossi, E., Zuffardi, O., Pistoia, V. & Pezzolo, A. (2011). Identification of novel prognostic markers in relapsing localized resectable neuroblastoma. *OMICS*, Vol.15, No.3, pp. 113-121.

Paulino, A.C. (2003). Palliative radiotherapy in children with neuroblastoma. *Pediatr Hematol Oncol*, Vol.20, No.2, pp. 111-117.

Pezzolo, A., Rossi, E., Gimelli, S., Parodi, F., Negri, F., Conte, M., Pistorio, A., Sementa, A., Pistoia, V., Zuffardi, O. & Gambini, C. (2009). Presence of 1q gain and absence of 7p gain are new predictors of local or metastatic relapse in localized resectable neuroblastoma. *Neuro Oncol*, Vol.11, No.2, pp. 192-200.

Ribatti, D., Raffaghello, L., Marimpietri, D., Cosimo, E., Montaldo, P.G., Nico, B., Vacca, A. & Ponzoni, M. (2003). Fenretinide as an anti-angiogenic agent in neuroblastoma. *Cancer Lett*, Vol.197, No.1-2, pp. 181-184.

Santana, V.M., Furman, W.L., McGregor, L.M. & Billups, C.A. (2008). Disease control intervals in high-risk neuroblastoma. *Cancer*, Vol.112, No.12, pp. 2796-2801.

Schulte, J.H., Bachmann, H.S., Brockmeyer, B., De Preter, K., Oberthuer, A., Ackermann, S., Kahlert, Y., Pajtler, K., Theissen, J., Westermann, F., Vandesompele, J., Speleman, F., Berthold, F., Eggert, A., Brors, B., Hero, B., Schramm, A. & Fischer, M. (2011). High ALK receptor tyrosine kinase expression supersedes ALK mutation as a determining factor of an unfavorable phenotype in primary neuroblastoma. *Clin Cancer Res*.

Seeger, R.C., Reynolds, C.P., Gallego, R., Stram, D.O., Gerbing, R.B. & Matthay, K.K. (2000). Quantitative tumor cell content of bone marrow and blood as a predictor of outcome in stage IV neuroblastoma: a Children's Cancer Group Study. *J Clin Oncol*, Vol.18, No.24, pp. 4067-4076.

Sharp, S.E., Shulkin, B.L., Gelfand, M.J., Salisbury, S. & Furman, W.L. (2009). 123I-MIBG scintigraphy and 18F-FDG PET in neuroblastoma. *J Nucl Med*, Vol.50, No.8, pp. 1237-1243.

Shaw, P.J. & Eden, T. (1992). Neuroblastoma with intracranial involvement: an ENSG Study. *Med Pediatr Oncol*, Vol.20, No.2, pp. 149-155.

Shusterman, S., London, W.B., Gillies, S.D., Hank, J.A., Voss, S.D., Seeger, R.C., Reynolds, C.P., Kimball, J., Albertini, M.R., Wagner, B., Gan, J., Eickhoff, J., DeSantes, K.B., Cohn, S.L., Hecht, T., Gadbaw, B., Reisfeld, R.A., Maris, J.M. & Sondel, P.M. (2010). Antitumor activity of hu14.18-IL2 in patients with relapsed/refractory neuroblastoma: a Children's Oncology Group (COG) phase II study. *J Clin Oncol*, Vol.28, No.33, pp. 4969-4975.

Simon, T., Berthold, F., Borkhardt, A., Kremens, B., De Carolis, B. & Hero, B. (2011). Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: results of German trials. *Pediatr Blood Cancer*, Vol.56, No.4, pp. 578-583.

Simon, T., Hero, B., Hunneman, D.H. & Berthold, F. (2003). Tumour markers are poor predictors for relapse or progression in neuroblastoma. *Eur J Cancer*, Vol.39, No.13, pp. 1899-1903.

Simon, T., Langler, A., Harnischmacher, U., Fruhwald, M.C., Jorch, N., Claviez, A., Berthold, F. & Hero, B. (2007). Topotecan, cyclophosphamide, and etoposide (TCE) in the treatment of high-risk neuroblastoma. Results of a phase-II trial. *J Cancer Res Clin Oncol*, Vol.133, No.9, pp. 653-661.

Sirachainan, N., Visudtibhan, A., Tuntiyatorn, L., Pakakasama, S., Chuansumrit, A. & Hongeng, S. (2008). Favorable response of intraommaya topotecan for leptomeningeal metastasis of neuroblastoma after intravenous route failure. *Pediatr Blood Cancer*, Vol.50, No.1, pp. 169-172.

Sofka, C.M., Semelka, R.C., Kelekis, N.L., Worawattanakul, S., Chung, C.J., Gold, S. & Fordham, L.A. (1999). Magnetic resonance imaging of neuroblastoma using current techniques. *Magn Reson Imaging*, Vol.17, No.2, pp. 193-198.

Stutterheim, J., Gerritsen, A., Zappeij-Kannegieter, L., Yalcin, B., Dee, R., van Noesel, M.M., Berthold, F., Versteeg, R., Caron, H.N., van der Schoot, C.E. & Tytgat, G.A. (2009). Detecting minimal residual disease in neuroblastoma: the superiority of a panel of real-time quantitative PCR markers. *Clin Chem*, Vol.55, No.7, pp. 1316-1326.

Stutterheim, J., Zappeij-Kannegieter, L., Versteeg, R., Caron, H.N., van der Schoot, C.E. & Tytgat, G.A. (2011). The prognostic value of fast molecular response of marrow disease in patients aged over 1 year with stage 4 neuroblastoma. *Eur J Cancer*, Vol.47, No.8, pp. 1193-1202.

Swerts, K., Ambros, P.F., Brouzes, C., Navarro, J.M., Gross, N., Rampling, D., Schumacher-Kuckelkorn, R., Sementa, A.R., Ladenstein, R. & Beiske, K. (2005). Standardization of the immunocytochemical detection of neuroblastoma cells in bone marrow. *J Histochem Cytochem*, Vol.53, No.12, pp. 1433-1440.

Taggart, D.R., Han, M.M., Quach, A., Groshen, S., Ye, W., Villablanca, J.G., Jackson, H.A., Mari Aparici, C., Carlson, D., Maris, J., Hawkins, R. & Matthay, K.K. (2009). Comparison of iodine-123 metaiodobenzylguanidine (MIBG) scan and [18F]fluorodeoxyglucose positron emission tomography to evaluate response after iodine-131 MIBG therapy for relapsed neuroblastoma. *J Clin Oncol*, Vol.27, No.32, pp. 5343-5349.

Vik, T.A., Pfluger, T., Kadota, R., Castel, V., Tulchinsky, M., Farto, J.C., Heiba, S., Serafini, A., Tumeh, S., Khutoryansky, N. & Jacobson, A.F. (2009). (123)I-mIBG scintigraphy in patients with known or suspected neuroblastoma: Results from a prospective multicenter trial. *Pediatr Blood Cancer*, Vol.52, No.7, pp. 784-790.

Villa, M.L., Ferrario, E., Trabattoni, D., Formelli, F., De Palo, G., Magni, A., Veronesi, U. & Clerici, E. (1993). Retinoids, breast cancer and NK cells. *Br J Cancer*, Vol.68, No.5, pp. 845-850.

Villablanca, J.G., Krailo, M.D., Ames, M.M., Reid, J.M., Reaman, G.H. & Reynolds, C.P. (2006). Phase I trial of oral fenretinide in children with high-risk solid tumors: a report from the Children's Oncology Group (CCG 09709). *J Clin Oncol*, Vol.24, No.21, pp. 3423-3430.

Viprey, V.F., Corrias, M.V., Kagedal, B., Oltra, S., Swerts, K., Vicha, A., Ladenstein, R. & Burchill, S.A. (2007). Standardisation of operating procedures for the detection of minimal disease by QRT-PCR in children with neuroblastoma: quality assurance on behalf of SIOPEN-R-NET. *Eur J Cancer*, Vol.43, No.2, pp. 341-350.

Wagner, L.M., Villablanca, J.G., Stewart, C.F., Crews, K.R., Groshen, S., Reynolds, C.P., Park, J.R., Maris, J.M., Hawkins, R.A., Daldrup-Link, H.E., Jackson, H.A. & Matthay, K.K. (2009). Phase I trial of oral irinotecan and temozolomide for children with relapsed high-risk neuroblastoma: a new approach to neuroblastoma therapy consortium study. *J Clin Oncol*, Vol.27, No.8, pp. 1290-1296.

Yanik, G.A., Parisi, M.T., Naranjo, A., Matthay, K.K., London, W.B., McGrady, P.W., Kreissman, S.G. & Shulkin, B.L. (2010). MIBG scoring as a prognostic indicator in patients with stage IV neuroblastoma: A COG study. *Journal of Clinical Oncology*, Vol.28, No.15s (abstract 9516).

Yu, A.L., Gilman, A.L., Ozkaynak, M.F., London, W.B., Kreissman, S.G., Chen, H.X., Smith, M., Anderson, B., Villablanca, J.G., Matthay, K.K., Shimada, H., Grupp, S.A., Seeger, R., Reynolds, C.P., Buxton, A., Reisfeld, R.A., Gillies, S.D., Cohn, S.L., Maris, J.M. & Sondel, P.M. (2010). Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med*, Vol.363, No.14, pp. 1324-1334.
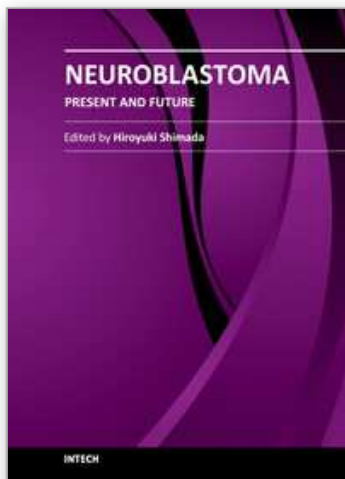
Neuroblastoma - Present and Future

Edited by Prof. Hiroyuki Shimada

Neuroblastoma, once called "enigmatic", due to "unpredictable" clinical behaviors, is composed of biologically diverse tumors. Molecular/genomic properties unique to the individual tumors closely link to the clinical outcomes of patients. Establishing risk stratification models after analyzing biologic characteristics of each case has made a great success in patient management. However, the trend of improving survival rates in neuroblastoma over the last 30 years has started to level off, and currently available treatment modalities have almost reached to their maximized intensity. Furthermore, aggressive treatment causes significant long-term morbidities to the survivors. We really need to make the next step to the level of personalized medicine with more precise understanding of neuroblastoma biology. This book includes useful data and insights from the world's experts in this field. I believe this book can make an excellent contribution to all the investigators working hard and fighting for the children stricken by this disease.

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