Neuroblastoma

Paradigm for Precision Medicine

Meredith S. Irwin, MD[a], Julie R. Park, MD[b,*]

KEYWORDS

- Neuroblastoma • Risk stratification • MYCN
- Segmental chromosome aberrations (SCA) • ALK (anaplastic lymphoma kinase)
- Phox2B • Myeloablative therapy (MAT) • Immunotherapy

KEY POINTS

- Neuroblastoma (NB) is the most common extracranial pediatric tumor, most frequently diagnosed cancer in infancy, and has a heterogeneous presentation and prognosis.
- Clinical and biological prognostic factors are used to risk stratify patients into groups with low, intermediate, and high risk for recurrence; most protocols now use the International Neuroblastoma Risk Group classification system.
- Age, stage, histology, and amplification of the *MYCN* oncogene are currently the most robust prognostic factors.
- Outcomes for low- and intermediate-risk NB are excellent, but survival for high-risk NB is less than 50%.
- High-risk NB tumors contain many segmental chromosome aberrations (eg, loss of heterozygosity 1p, 11q); but recurrent somatic mutations are rare, with anaplastic lymphoma kinase (*ALK*) being the most commonly altered gene in approximately 10% of NB.
- Survival after relapse of metastatic NB is uncommon; current and upcoming trials will rely on incorporation of novel immunotherapies, inhibitors of aberrant pathways (eg MYC, ALK), and radioisotope-containing regimens, such as high-dose iodine-131-metaiodobenzylguanidine.

INTRODUCTION

Neuroblastoma (NB), the most common extracranial tumor of childhood, is a cancer of primordial neural crest cells that give rise to sympathetic neural ganglia and adrenal medulla. NB has a diverse pattern of clinical presentation and prognosis that ranges

[a] Division of Hematology-Oncology, Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON M5G1X8, Canada; [b] Division of Hematology-Oncology, Seattle Children's Hospital, University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, 4800 Sandpoint Way NE, Seattle, WA 98105, USA
* Corresponding author.
E-mail address: julie.park@seattlechildrens.org

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from spontaneous regression to aggressive metastatic tumors. For more than 2 decades, NB treatment has served as a paradigm for the incorporation of clinical and biological factors to stratify patients and tailor therapies. Using clinical, pathologic, and increasingly genetic factors, patients can be categorized as low, intermediate (IR), and high risk (HR) for recurrence. The overall survival (OS) for patients with low and IR NB is excellent at greater than 90% with relatively minimal surgical or medical interventions (**Fig. 1**). The goal of recent trials for non-HR patients has been to decrease treatments further and minimize chemotherapy-related toxicities. In contrast, long-term survival for HR patients remains 40% to 50% despite intensification of treatments and incorporation of immunotherapies. Current protocols are aimed at identifying better predictors of response and outcome as well as discovering genetic aberrations that may represent tractable therapeutic targets. This article summarizes the clinical presentations and current understanding of NB biology and prognostic features, their roles in risk stratification–based treatments, and novel therapies for patients with recurrent disease.

EPIDEMIOLOGY AND GENETIC PREDISPOSITION

The incidence of NB in North America and Europe is 10.5 per million children between 0 and 14 years of age, with a slight male predominance (1.2:1.0).[1–4] NB is the most common cancer diagnosed in infancy, with most patients diagnosed between 0 and 4 years of age (median age 19 months[5]), and less than 5% at greater than 10 years. NB accounts for 8% to 10% of all pediatric cancers and 12% to 15% of cancer-related deaths in children. Although there are no significant geographic variations in incidence, there are ethnic disparities in outcome. African American and Native American patients are more likely to have HR features and poor outcomes, in part because of genetic differences.[6–8] Environmental factors, including parental exposures, have not been clearly linked with NB development.[9,10]

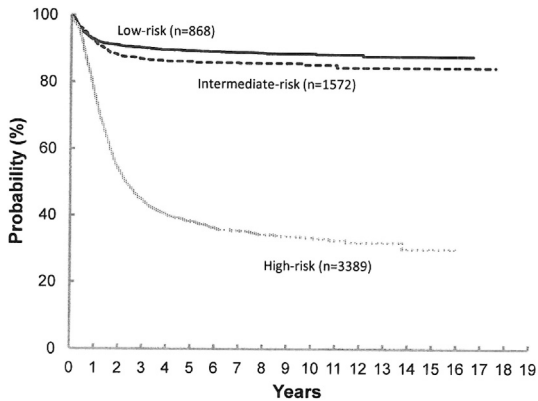

Fig. 1. Event-free survival (EFS) based on children's oncology group (COG) risk stratification. EFS Kaplan-Meier survival curves calculated from the time of diagnosis for children enrolled onto COG (since 2001); Children's Cancer Group and Pediatric Oncology Group Neuroblastoma Biology trials and were classified as low risk, IR, or HR at the time of diagnosis based on clinical and biological factors (current COG classification is summarized in **Table 2**). (*From* Park JR, Bagatell R, London WB, et al. Children's Oncology Group 2013 blueprint for research: neuroblastoma. Pediatr Blood Cancer 2013;60(6):986, with permission. © 2012 Wiley Periodicals, Inc.)