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REVIEW ARTICLE

Advances in Risk Classification and Treatment Strategies for Neuroblastoma

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ABSTRACT

Risk-based treatment approaches for neuroblastoma have been ongoing for decades. However, the criteria used to define risk in various institutional and cooperative groups were disparate, limiting the ability to compare clinical trial results. To mitigate this problem and enhance collaborative research, homogenous pretreatment patient cohorts have been defined by the International Neuroblastoma Risk Group classification system. During the past 30 years, increasingly intensive, multimodality approaches have been developed to treat patients who are classified as high risk, whereas patients with low- or intermediate-risk neuroblastoma have received reduced therapy. This treatment approach has resulted in improved outcome, although survival for high-risk patients remains poor, emphasizing the need for more effective treatments. Increased knowledge regarding the biology and genetic basis of neuroblastoma has led to the discovery of druggable targets and promising, new therapeutic approaches. Collaborative efforts of institutions and international cooperative groups have led to advances in our understanding of neuroblastoma biology, refinements in risk classification, and stratified treatment strategies, resulting in improved outcome. International collaboration will be even more critical when evaluating therapies designed to treat small cohorts of patients with rare actionable mutations.

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INTRODUCTION

Neuroblastoma is notable for its broad range of clinical behaviors. Tailored treatment approaches, based on the presence or absence of specific clinical and biologic factors, have been used for decades, and successive institutional and cooperative group risk-based clinical trials have led to substantial improvement in outcome for patients classified as low or intermediate risk. Progress has also been made in the treatment for high-risk neuroblastoma, although the outcome for patients with this clinical phenotype still remains poor, with long-term survival $< 50\%$. In concert with the cooperative group clinical trial efforts, large numbers of clinically annotated tumor and germline samples have been collected and banked for research studies. Genomic interrogation of these tissues has led to significant advances in our understanding of neuroblastoma epidemiology and biology. In this review, we discuss the major accomplishments in risk classification and stratified treatment approaches that have resulted from national and international collaborative research. We also highlight recent discoveries that have increased our knowledge regarding the genetic basis of neuroblastoma, and we provide an overview of an expanding portfolio of promising therapies that target actionable genomic mutations.

RISK CLASSIFICATION

Clinical heterogeneity is a hallmark of neuroblastoma. In an effort to guide risk-based treatment for patients with neuroblastoma, pediatric cooperative groups developed classification systems that were based on combinations of clinical and biologic prognostic markers. However, criteria used to define risk varied significantly among the cooperative groups, limiting the ability to compare clinical trial results. To address this problem, a task force, representing the major pediatric cooperative groups around the world, was formed in 2004 to develop an international pretreatment risk algorithm. The International Neuroblastoma Risk Group (INRG) classification system was based on analyses of data collected on more than 8,800 patients diagnosed between 1990 and 2002 in North American, Europe, Japan, and Australia.[1] The system uses combinations of seven prognostic risk factors to define 16 pretreatment groups stratified by these prognostic markers (labeled A to R; Table 1). The 8,800 patients

Table 1. International Neuroblastoma Risk Group Pretreatment Classification Schema

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing, GNB intermixed					A (very low)
L1		Any, except GN maturing or GNB intermixed		NA			B (very low)
				Amplified			K (high)
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D (low)
					Yes		G (intermediate)
	≥ 18	GNB nodular neuroblastoma	Differentiating	NA	No		E (low)
					Yes		H (intermediate)
			Poorly differentiated or undifferentiated	NA			H (intermediate)
				Amplified			N (high)
M	< 18			NA		Hyperdiploid	F (low)
	< 12			NA		Diploid	I (intermediate)
	12 to < 18			NA		Diploid	J (intermediate)
	< 18			Amplified			O (high)
	≥ 18						P (high)
MS	< 18			NA	No		C (very low)
					Yes		Q (high)
				Amplified			R (high)

Abbreviations: GN, ganglioneuroma; GNB, ganglioneuroblastoma; INRG, International Neuroblastoma Risk Group; NA, not amplified.

were categorized as belonging to a very low–, low-, intermediate-, or high-risk group, based on the 5-year event-free survival (EFS) rates of the 16 pretreatment groups.

A new staging system was required for the INRG classification system,[2] because the surgical and pathologic criteria used to determine International Neuroblastoma Staging System (INSS) stage are not compatible with pretreatment classification. The INRG staging system is based on imaging criteria, and the extent of locoregional disease is determined by the absence or presence of image-defined risk factors (L1 and L2, respectively). Stage M indicates the presence of disseminated disease, analogous to INSS stage 4, and stage MS is similar to INSS stage 4S tumors, with metastases limited to skin, liver, and bone marrow without cortical bone involvement, but with no limitation on the size of the primary tumor.

The INRG Task Force also developed consensus guidelines for molecular diagnostics,[3] detection of minimal disease in bone marrow, blood, and stem-cell preparations,[4] and imaging and staging.[5,6] Although the task force recognized that genome-wide studies had led to powerful new predictors of outcome, microarray analyses of DNA copy number alterations and gene expression were not widely available at the time the INRG classification system was established, and only a few annotated genetic alterations were included in the classification system. It is anticipated that the next-generation INRG classification system will provide more precise prognostication by incorporating profiles of the neuroblastoma genome, transcriptome, and epigenome.

CLINICAL ADVANCES IN RISK-STRATIFIED NEUROBLASTOMA THERAPY

Table 2 summarizes the findings of selected cooperative group clinical trials conducted during the past three decades that have influenced clinical management.

Treatment of Low- and Intermediate-Risk Disease

Patients with low- or intermediate-risk neuroblastoma have excellent outcomes, and a series of cooperative group trials evaluating reductions in therapy using risk-based treatment approaches for these children has led to decreased therapy-related toxicities and improved outcome. In the low-risk COG P9641 study (Children's Oncology Group P9641; ClinicalTrials.gov identifier NCT00003119), a 5-year overall survival (OS) rate (± standard deviation [SD]) of 96% ± 1% was achieved with surgery alone for patients with asymptomatic INSS stage 2a or 2b tumors.[7] For low-risk patients with INSS stage 1 or 4s neuroblastoma, 5-year OS rates were 99% ± 1% and 91% ± 1%, respectively. Similarly, the SIOPEN LNESG1 study (International Society of Pediatric Oncology European Neuroblastoma Research Network Localized Neuroblastoma European Study) demonstrated that surgery alone, even in those with less than a complete resection, was curative in nearly all patients.[8] Furthermore, observational studies have demonstrated that subsets of infants with localized tumors can be cured without any treatment, including surgery.[9,10]

In the intermediate-risk COG A3961 study (ClinicalTrials.gov identifier NCT00003093), a 3-year OS rate (± SD) of 96% ± 1% was observed with substantial reductions in the duration of treatment and dose of chemotherapeutic agents compared with regimens used in earlier clinical trials.[11] SIOPEN studies have also demonstrated excellent survival rates in infants with unresectable tumors or disseminated neuroblastoma without *MYCN* amplification with reduced treatment.[12,13] The efficacy of decreased chemotherapy without radiotherapy was also evaluated by SIOPEN in children age > 1 year with unresectable neuroblastoma lacking *MYCN* amplification.[14] OS for this cohort was excellent with this reduced treatment approach. However, outcome was significantly inferior for patients with tumors classified as having unfavorable histology according to the International Neuroblastoma Pathology Classification System,[24] indicating that a more intensive regimen including radiotherapy is warranted for older patients with unresectable tumors of unfavorable histology. The

Table 2. Patient Characteristics and Treatment Results From Selected Clinical Trials

Study Group	Patient Cohort	Years of study	No. of patients	Age Range	EFS (%)*	OS (%)*	Study Question	Data source
COG P9641	Low risk	1998 to 2004	915	0 to 21 years	89 ± 1 (5 Years)	97 ± 1 (5 Years)	Surgery alone for localized tumors	Strother et al[7]
SIOPEN LNESG1	*MYCN* nonamplified, localized, resectable	1995 to 1999	288 (stage 1) 123 (stage 2)	0 to 20 years	94.3 ± 2.7 (5 years [RFS]) 82.8 ± 6.7 (5 years [RFS])	98.9 ± 1.1 (5 Years) 93.2 ± 4.6 (5 Years)	Surgery alone for localized tumors	De Bernardi et al[8]
COG ANBL00P2	Low risk	2001 to 2010	87	0 to 6 months	97.7 ± 2.2 (3 Years)	100 (3 Years)	Observation alone	Nuchtern et al[9]
GPOH NB95-S and 97	Infants with localized disease	1995 to 2004	93	< 12 months	56 ± 5 (5 Years)	99 ± 1 (5 Years)	Observation alone of unresected tumors	Hero et al[10]
COG A3961	Intermediate risk	1997 to 2005	479	0 to 21	88 ± 2 (3 Years)	96 ± 1 (3 Years)	Risk-based treatment reduction	Baker et al[11]
SIOPEN 99.1	*MYCN* nonamplified, localized, unresectable	1999 to 2004	120	< 12 months	90 ± 3 (5 Years)	99 ± 1 (5 Years)	Risk-based treatment reduction	Rubie et al[12]
SIOPEN 99.2	*MYCN* nonamplified, disseminated	1999 to 2004	170	< 12 months	88.7 ± 5.9 (5 Years)	95.7 ± 3.7 (5 Years)	Risk-based treatment reduction	De Bernardi et al[13]
SIOPEN 99.2	*MYCN* nonamplified, localized, unresectable	2001 to 2006	160	> 12 months	76.4 ± 6	87.6 ± 4.5	Risk-based treatment reduction	Kohler et al[14]
CCLG-NB-1990-11	Children with stage 4 disease	1990 to 1999	262	> 12 months	30.2 (5 Years)	31.5 (5 Years)	OPEC/OJEC *v* **rapid COJEC**	Pearson et al[15]
ENSG1	Children with stage 3 or 4 disease responsive to induction chemotherapy	1982 to 1985	65	All	38 ± 17 (5 Years)	47 ± 17 (5 Years)	**HDT melphalan consolidation** *v* no further treatment	Pritchard et al[16]
IGR 1980-1996	High risk	1980 to 1996	218	< 12 months	29 ± 6 (5 Years)	31 ± 6 (5 Years)	Prognosis factors after HDT	Hartmann et al[17]
CCG 3891	High risk	1991 to 1996	539	1 to 18 years	30 ± 4 (5 Years) 42 ± 5 (5 Years)	39 ± 4 (5 Years) 50 ± 5 (5 Years)	**HDT** *v* CC Time from second random assignment: *cis*-**RA** *v* no *cis*-RA	Matthay et al[18,19]
GPOH NB97	High risk	1997 to 2002	295	0 to 20 years	47 ± 8 (3 Years)	62 ± 8 (3 Years)	**HDT** *v* CC	Berthold et al[20]
COG A3973	High risk	2001 to 2006	486	< 30 years	38 ± 4 (5 Years)	50 ± 4.5 (5 Years)	Immunomagnetic purging of ABMT product	Kreissman et al[21]
SIOPEN HR-NBL1	High risk	2002 to 2011	598	1 to 18 years	49 (3 Years)	60 (3 Years)	HDT with **BuMel** *v* CEM	Ladenstein et al[22]
COG ANBL0032	High risk	2002 to present	225	0 to 30 years	66 ± 5 (2 Years)	86 ± 4 (2 Years)	**ch14.18 + GM-CSF/IL-2 + *cis*-RA** *v* *cis*-RA	Yu et al[23]

NOTE. Bold font indicates superior trial arm.

Abbreviations: ABMT, autologous bone marrow transplantation; BuMel, busulfan plus melphalan; CC, continuing chemotherapy; CCG, Children's Cancer Group; CCLG, Children's Cancer and Leukaemia Group; CEM, carboplatin, etoposide, and melphalan; COG, Children's Oncology Group; COJEC, cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide every 10 days; EFS, event-free survival; ENSG, European Neuroblastoma Study Group; GM-CSF, granulocyte macrophage colony-stimulating factor; GPOH, German Society of Pediatric Oncology and Hematology; HDT, high-dose therapy; IGR, Institut Gustave Roussy; IL-2, interleukin-2; OJEC, vincristine, carboplatin, etoposide, and cyclophosphamide every 21 days; OPEC, vincristine, cisplatin, etoposide, and cyclophosphamide every 21 days; OS, overall survival; RA, retinoic acid; RFS, relapse-free survival; SCT, stem-cell transplantation; SIOPEN, International Society of Paediatric Oncology Europe Neuroblastoma.

*Rate ± standard deviation.

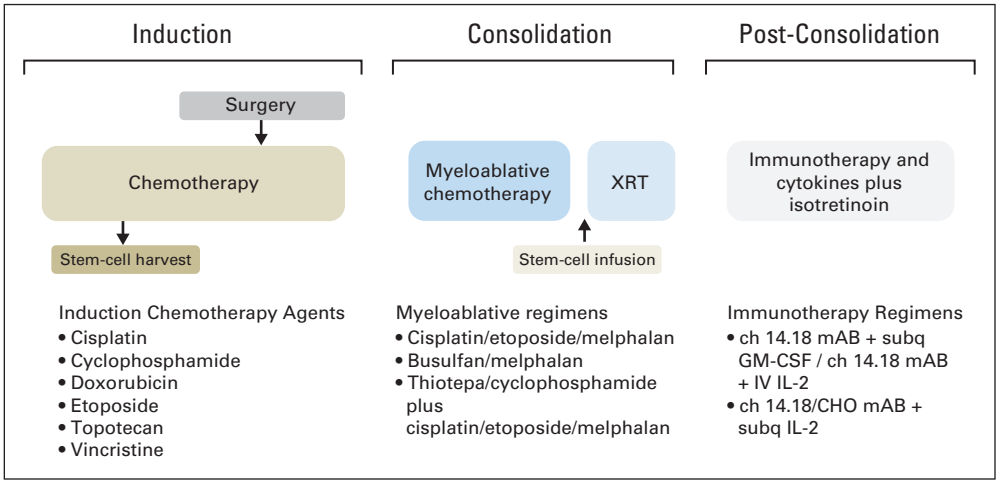

Fig 1. Current standard-of-care treatment strategy for high-risk neuroblastoma. Therapy consists of three treatment blocks: induction (chemotherapy and primary tumor resection); consolidation (high-dose chemotherapy with autologous stem-cell rescue and external-beam radiotherapy [XRT]); and postconsolidation (anti–ganglioside 2 immunotherapy with cytokines and *cis*-retinoic acid). ch, chimeric; CHO, Chinese hamster ovary; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-2, interleukin-2; IV, intravenous; mAB, monoclonal antibody.

impact of additional decreases in therapy intensity for specific subsets of patients is being evaluated in the current COG study for non–high-risk disease, ANBL1232 (ClinicalTrials.gov identifier NCT02176967), and the SIOPEN LINES trial (Low- and Intermediate-Risk Neuroblastoma European Study; ClinicalTrials.gov identifier NCT01728155).

Treatment of High-Risk Disease

Modern high-risk treatment regimens include five to six cycles of induction chemotherapy and surgery, consolidation therapy with high-dose therapy (HDT) with autologous hematopoietic stem-cell rescue and irradiation, and postconsolidation therapy to treat minimal residual disease (Fig 1).

Induction and consolidation. On the basis of evidence indicating that increased dose-intensity may overcome chemotherapy resistance,[25] more recent high-risk clinical trials have incorporated higher doses of chemotherapeutic agents and decreased interval time between cycles of therapy during induction. A randomized European clinical trial demonstrated improved EFS with a 10-day interval between treatments compared with a 21-day interval. However, no significant difference in OS was observed between the rapid and standard regimens.[15] Consolidation therapy has also been intensified for high-risk patients, with the introduction of HDT regimens with stem-cell transplantation in 1980s.[16] In 1999, a randomized Children's Cancer Group (CCG) phase III cooperative group study demonstrated that HDT with autologous bone marrow rescue resulted in significantly better EFS than nonmyeloablative chemotherapy (3-year EFS ± SD, 34% ± 4% *v* 22% ± 4%; $P = .034$).[18] Although no significant difference in OS was observed (5-year OS ± SD, 43% ± 4% *v* 44% ± 4%; $P = .87$),[18] HDT with stem-cell rescue had been considered an integral part of standard-of-care therapy for children with high-risk neuroblastoma subsequent to the publication of this seminal clinical trial.

A reanalysis of the CCG cohort after longer follow-up continued to show a significantly better EFS rate for the patients randomly assigned to receive HDT with autologous bone marrow rescue compared with patients randomly assigned to the nonmyeloablative chemotherapy arm (5-year EFS ± SD, 30% ± 4% *v* 19% ± 3%; $P = .04$). However, no statistically significant improvement in OS was observed (5-year OS ± SD, 39% ± 4% *v* 30% ± 4%; $P = .39$).[19] An improvement in EFS (3-year EFS ± SD, 47% ± 8% *v* 31% ± 8%; $P = .02$), but not OS (3-year OS ± SD, 62% ± 6% *v* 53% ± 8%; $P = .08$), was also reported with HDT and autologous stem-cell rescue compared with maintenance chemotherapy in an intent-to-treat analysis of a randomized clinical trial conducted by the German Society of Pediatric Oncology and Hematology (GPOH).[20] Similar results were observed in a recent update of a meta-analysis evaluating HDT and stem-cell transplantation in a cohort of 739 high-risk patients.[26] Although the delay in time from diagnosis to tumor progression or relapse is clinically important, these results emphasize the need for new treatment strategies that will ultimately improve OS.

In a more recent randomized COG study (A3973; ClinicalTrials.gov identifier NCT0004188), all patients received HDT with carboplatin, etoposide, and melphalan (CEM) and stem-cell rescue, and the impact of immunomagnetic peripheral-blood stem-cell (PBSC) purging was evaluated.[21] No significant difference in outcome was seen between the randomly assigned cohorts receiving immunomagnetic purged versus nonpurged PBSC rescue. However, EFS and OS rates for the entire cohort were superior to those in the previous CCG study (38% [95% CI, 34% to 42%] and 50% [95% CI, 46% to 55%] at 5 years, respectively).[21] On the basis of the promising results of a pilot study evaluating two cycles of HDT and stem-cell rescue in rapid succession,[27] the COG designed a randomized phase III study (ANBL0532; ClinicalTrials.gov identifier NCT00567567) to compare the efficacy of two cycles of HDT (thiotepa plus cytoxan and CEM) plus stem-cell rescue with one cycle (CEM). The results of this trial, which are expected to be available in the next few months (A. Naranjo, personal communication, December 2014), will determine if this intensified consolidation therapy strategy will further improve outcome.

On the basis of the Gustave Roussy[17] experience with busulfan plus melphalan, the efficacy of this regimen has been compared with that of CEM in a randomized phase III trial conducted by SIOPEN. Superior EFS and OS were observed with busulfan plus melphalan compared with CEM.[22] The busulfan plus melphalan regimen was also associated with less toxicity, although the incidence of sinusoidal obstructive syndrome was higher. A COG pilot study (ANBL12P1; ClinicalTrials.gov identifier NCT01798004) to evaluate the feasibility of administering busulfan plus melphalan and stem-cell rescue after an induction chemotherapy used in previous COG studies is ongoing. The COG is also conducting a pilot study (ANBL09P1; ClinicalTrials.gov identifier

NCT01175356) testing the combination of iodine-131 (^{131}I) plus metaiodobenzylguanidine (MIBG) with stem-cell rescue followed by busulfan plus melphalan and stem-cell support. ^{131}I-MIBG therapy will be evaluated in a randomized phase III trial in patients with newly diagnosed high-risk neuroblastoma if the pilot study demonstrates safety and feasibility. The benefits of a further intensified consolidation regimen will also be evaluated in patients with a poor response to induction treatment in the VERITAS SIOPEN study comparing tandem cycles of HDT with thiotepa and busulfan plus melphalan with stem-cell rescue versus ^{131}I-MIBG with stem-cell rescue followed by busulfan plus melphalan and stem-cell support.

Postconsolidation. Half of all patients who achieve a clinical remission after induction and consolidation therapy will relapse, indicating the presence of therapy-resistant minimal residual disease. Efforts to treat residual disease after consolidation therapy with isotretinoin were first evaluated in the 1990s, and a randomized COG trial demonstrated that treatment with this differentiating agent improved EFS compared with no treatment.[18] However, OS was not significantly improved,[18] and no difference in either EFS or OS was observed with further follow-up.[19] A subsequent, seminal randomized COG study demonstrated significant improvement in both EFS and OS with a postconsolidation regimen of immunotherapy, consisting of anti–ganglioside 2 (GD2) chimeric 14.18 antibody and cytokines plus isotretinoin compared with isotretinoin alone (2-year EFS ± SD, 66% ± 5% *v* 46% [plusmn 5% [$P = .01$]; 2-year OS ± SD, 86% ± 4% *v* 75% ± 5% [$P = .02$].[15]

Improved Survival of High-Risk Patients by Era

A retrospective analysis of survival of 3,352 patients with high-risk neuroblastoma diagnosed between 1990 and 2010 who were enrolled onto the COG ANBL00B1 study supports the sequential dose-intensification strategies that have been used in successive North American and European cooperative group clinical trials. Using a data freeze date of December 31, 2013, survival rates were determined to be significantly different according to diagnostic era ($P < .001$), with better outcome observed for patients diagnosed after 2000, when consolidation with HDT and stem-cell rescue was routinely included in the treatment plan for high-risk patients (Fig 2). Only 6% (64 of 1,015) of the patients diagnosed between 2000 and 2004 and 30% (445 of 1,484) of those diagnosed between 2005 and 2010 received immunotherapy and cytokines plus isotretinoin after consolidation. Postconsolidation treatment with immunotherapy and cytokines plus isotretinoin is now considered part of standard-of-care treatment, and a further improvement in OS is anticipated for the cohort of high-risk patients diagnosed and treated after 2010.

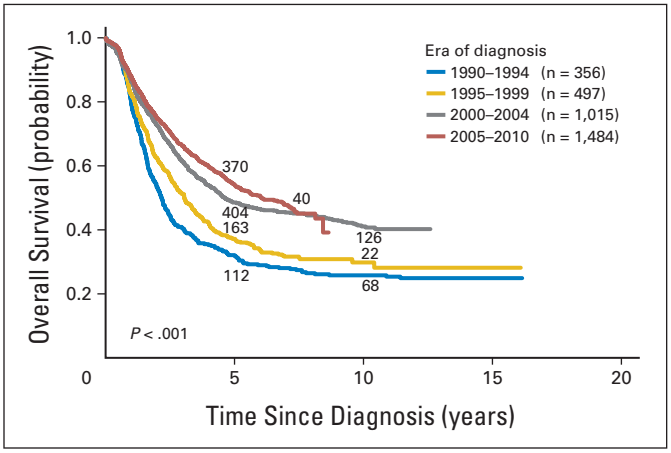

Fig 2. Probability of overall survival (OS) among 3,352 Children's Oncology Group (COG) patients with high-risk neuroblastoma diagnosed between 1990 and 2010 according to era. Five-year OS rates (+ SE) for patients diagnosed between 1990 and 1994 (n = 356), 1995 to 1999 (n = 497), 2000 to 2004 (n = 1,015), and 2005 to 2010 (n = 1,484) are 29% + 0.02, 34% + 0.02, 47% + 0.02, and 50% + 0.02, respectively. Data from COG Statistics and Data Center.

BIOLOGIC ADVANCES

The efforts to collect and bank large numbers of clinically annotated tumor and germline samples for research studies by the cooperative groups have enabled major advances in our understanding of the genetic basis of neuroblastoma, more precise prognostication, and the discovery of therapeutic targets.

Inherited Genetic Determinants

Inherited mutations in *PHOX2B*[28] and *ALK*[29] have been identified in small numbers of familial neuroblastoma cases. However, for the majority of patients, these predisposition genes do not play a causative role in neuroblastoma oncogenesis. Genome-wide association studies have demonstrated that for patients with sporadic tumors, disease susceptibility and neuroblastoma phenotype are influenced by common genetic variants. Single-nucleotide polymorphisms (SNPs) in *DUSP12*, *HSD17B12*, and the *DDX4/IL31RA* locus at chromosome 5q11.2 are associated with susceptibility to low-risk neuroblastoma, whereas SNPs within or upstream of *CASC15* and *CASC14* on chromosome 6p22, *BARD1*, *LMO1*, *HACE1*, and *LIN28B* as well as a common copy-number variation at 1q21 within *NBPF23* have been shown to be highly enriched in the cohort of patients with clinically aggressive, high-risk disease.[30,31] African genomic ancestry has also been shown to be significantly associated with high-risk neuroblastoma, supporting a genetic etiology for the racial disparities in survival observed in neuroblastoma.[32,33] Furthermore, SNPs within *CASC15*, *CASC14*, and *SPAG16*, which are highly associated with high-risk disease, have higher risk-allele frequencies in the African American cohort.[33] More recent efforts, focused on the identification of rare susceptibility SNPs, have demonstrated that two rare germline *TP53* variants are also highly associated with neuroblastoma.[34] Additional sequencing studies will undoubtedly lead to the discovery of new risk variants and a deeper understanding of the genetic etiology of neuroblastoma.

Refined Prognostication

Cooperative group collaborations have also made it possible to conduct whole-genome copy-number and expression studies with large numbers of tumors and validate the findings within independent cohorts. These studies have led to the discovery of expression profiles and copy-number changes that are capable of substratifying patients currently classified as low, intermediate, or high risk. Both genome-wide profiles[35-37] and pathway-specific profiles focused on hypoxia,[38] MYCN downstream targets,[39] or inflammation[40] have shown independent prognostic value in multivariable analyses. In addition, whole-genome microRNA[41] and gene promoter methylation[42] profiling are also capable of refining current risk group classifications. Ongoing low- and intermediate-risk cooperative group trials in North America and Europe are now stratifying treatments according to genomic copy-number profile, and molecular signatures will be evaluated in the next generation of studies.[43]

Molecular Therapeutic Targets

The identification of somatic alterations in high-risk tumors and an increased understanding of how these mutations drive tumor growth have provided strong rationale for evaluating specific molecularly targeted therapeutics. The most common somatic alteration in neuroblastoma is amplification of the *MYCN* oncogene. Although *MYCN* has been difficult to therapeutically target, preclinical data have shown that *MYCN* transcription can be downregulated through bromodomain and extraterminal (BET) domain bromodomain inhibition[44] (Fig 3). Additional studies have demonstrated that PI3[45]or Aurora A[46] kinase inhibition will destabilize the MYCN protein. The Aurora A kinase inhibitor MLN8237 is currently being evaluated in combination with irinotecan and temozolomide in a phase I study by the New Approaches to Neuroblastoma Therapy (NANT) consortium (NANT2009-03; ClinicalTrials.gov identifier NCT01601535). Ongoing efforts are directed to design an optimal Aurora A kinase inhibitor of MYCN. An inhibitor of a key downstream target of MYCN, ornithine decarboxylase, is also being tested in early-phase neuroblastoma trials (NANT2012-01; ClinicalTrials.gov identifier NCT02030964).

Approximately 14% of newly diagnosed high-risk neuroblastomas bear activating *ALK* mutations or gene amplifications,[47] and subclonal or acquired *ALK* mutations may arise in relapsed neuroblastoma.[48] The combined MET/anaplastic lymphoma kinase (ALK) inhibitor crizotinib generated significant excitement as a rational therapeutic target for ALK-aberrant tumors. A COG phase I study (ADVL0912; ClinicalTrials.gov identifier NCT00939770) evaluating single-agent crizotinib in advanced pediatric solid tumors revealed disappointing response rates in patients with neuroblastoma. Only 9% of patients with neuroblastoma with known ALK-aberrant tumors and 6% of those with unknown *ALK* status achieved ≥ partial

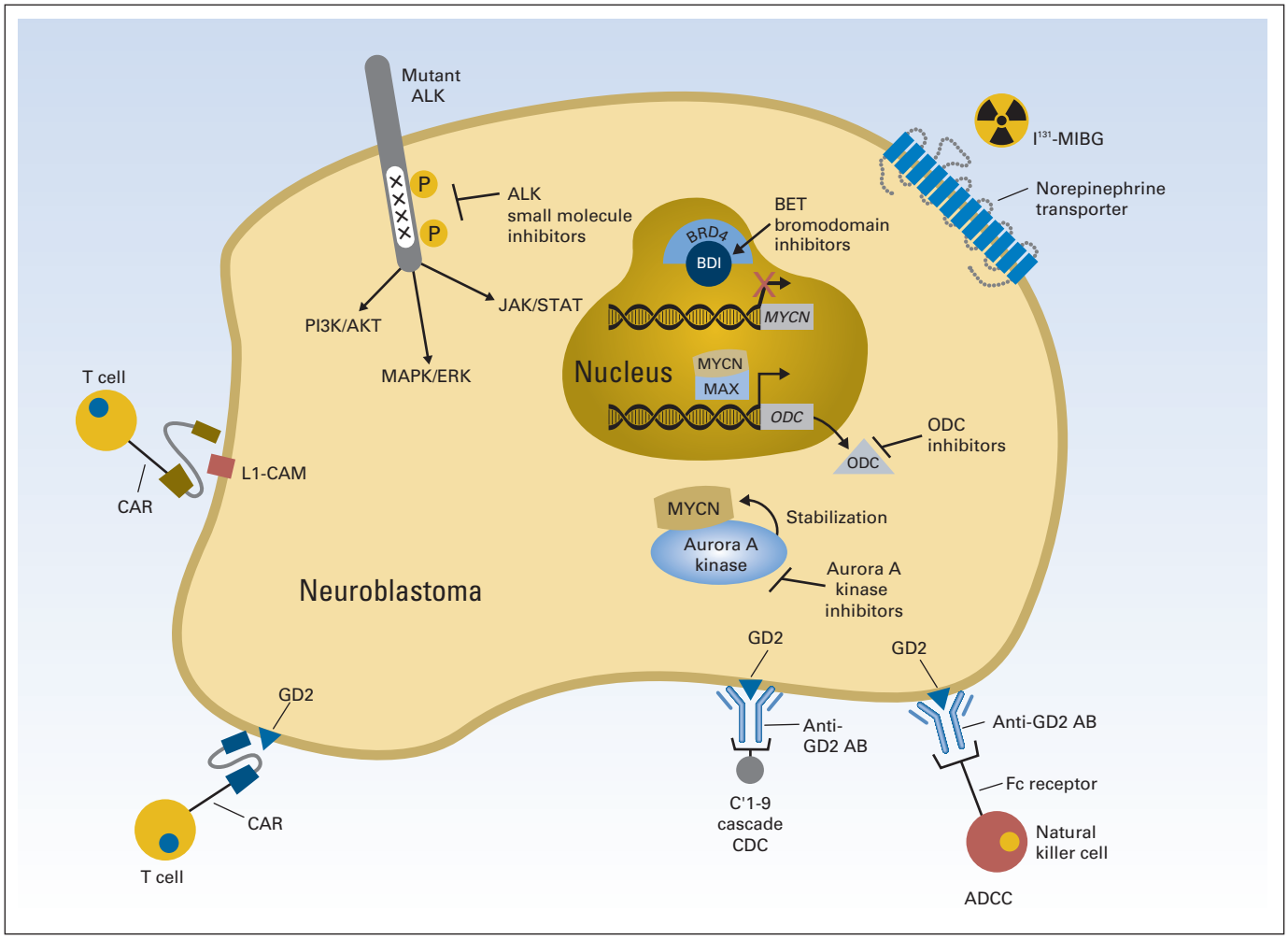

Fig 3. Current clinical approaches in targeting neuroblastoma. Iodine-131 (^{131}I) plus metaiodobenzylguanidine (MIBG) is carried through norepinephrine transporter allowing for targeted radiotherapy. Small-molecule inhibitors of anaplastic lymphoma kinase (ALK) selectively bind constitutively phosphorylated mutant *ALK* receptors, leading to decreased signaling through phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK)/extracellular regulated kinase (ERK), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways. Bromodomain and extraterminal domain (BET) bromodomain inhibitors (BDI) bind BRD4 protein, preventing DNA binding and transcription of *MYCN*. MYCN/MAX transcription complex directly targets ornithine decarboxylase (ODC), rate-limiting enzyme in production of polyamines, which plays role in cell replication, translation, growth, and survival. ODC inhibitors such as antihelmenthic agent difluoromethylornithine (DFMO) reduce polyamine synthesis. Aurora kinase inhibitors reduce ability of aurora kinase to bind to and stabilize MYCN protein, leading to its degradation. Immunotherapeutic approaches include use of chimeric antigen receptor (CAR) T cells against both L1-CAM and ganglioside 2 (GD2) cell surface antigens to promote host antitumor response. Anti-GD2 antibodies (ABs) bind GD2 and cause cell death by activating both complement-dependent cytotoxicity (CDC) and AB-dependent cellular cytotoxicity (ADCC) from natural-killer cells.

response.[49] Common *ALK* mutations in neuroblastoma, such as F1174L, seem to be relatively resistant to standard crizotinib doses, which might be overcome by increased doses.[50] A COG phase I pediatric study testing crizotinib in combination with topotecan and cyclophosphamide is ongoing (ADVL1212; ClinicalTrials.gov identifier NCT01606878), and second-generation *ALK* inhibitors such as RXDX-1 (ClinicalTrials.gov identifier NCT02097810) and LDK378 (ClinicalTrials.gov identifier NCT01742286) are in early clinical development or early-phase trials in North America and Europe.

Nearly half of adolescents and young adults with neuroblastoma bear somatic mutations in *ATRX*,[51] a gene that plays a role in regulating chromatin remodeling, nucleosome assembly, and telomere maintenance.[52] These patients may benefit from inhibitors that target these pathways, but preclinical and clinical studies are needed to confirm the efficacy of these approaches.

Because next-generation sequencing efforts have demonstrated that neuroblastoma tumors harbor few mutations, large cohorts of patients with neuroblastoma will be required to determine optimal strategies for implementing targeted treatment in different patient subsets.

ADDITIONAL TARGETED TREATMENT APPROACHES

Radiopharmaceutical Targeted Therapies

^{131}I-MIBG, a β particle–emitting norepinephrine analog taken up preferentially by cells expressing the norepinephrine transporter (Fig 3), represents one of the earliest and most successful targeted therapies for relapsed neuroblastoma.[53] The vast majority of neuroblastoma tumors are ^{131}I-MIBG avid, allowing for targeted radiotherapy to sites of active disease. Studies conducted in the 1990s showed promise, with response rates ranging from 21% to 47% and minimal nonhematologic toxicities. ^{131}I-MIBG doses $>$ 12 mCi/kg have been associated with improved response rates compared with lower doses, and autologous PBSC support has allowed for dose escalations of up to 18 mCi/kg. Tandem ^{131}I -MIBG therapies and combination treatments with high-dose chemotherapy have also been evaluated in early-phase studies.[53]

As a means to increase the effective dose, ^{131}I-MIBG has also been administered without contaminating nonradioactive MIBG (no carrier–added ^{131}I-MIBG)[54] or in combination with radiosensitizers, including vincristine plus irinotecan[55] or vorinostat.[53] Recently, the NANT consortium developed a randomized selection-design phase II trial evaluating ^{131}I-MIBG alone versus ^{131}I-MIBG plus vorinostat or vincristine and irinotecan (NANT2011-01; ClinicalTrials.gov identifier NCT02035137). Novel radiolabeled molecules for patients with ^{131}I-MIBG–nonavid or –nonresponsive disease, such as lutetium-177–DOTATATE, are also in the early stages of development.[56]

Antiangiogenic Approaches

On the basis of the observation that tumor growth in preclinical neuroblastoma models can be inhibited with antiangiogenic agents, the phase II BEACON (Bevacizumab With Temozolomide $\pm$ Irinotecan for Neuroblastoma in Children) trial (Eudract identifier 2012-000072-42; ClinicalTrials.gov identifier NCT40708286) is testing the activity of bevacizumab combined with chemotherapy (temozolomide or irinotecan plus temozolomide) in children with relapsed or refractory neuroblastoma. This study will provide the foundation for an international multiarm multistage study design that will be used across Europe to evaluate the activity of new drugs.

Immunotherapeutic Targeted Treatments

The positive impact of passive immunotherapy with anti-GD2 antibodies 3F8 and chimeric 14.18 in high-risk neuroblastoma has led to a surge in development of additional immunotherapeutic modalities for patients with neuroblastoma. Humanized 14.18 linked to interleukin-2 has shown promising activity in patients without measurable disease on computed tomography scan (marrow- or MIBG-avid disease only), with a complete response rate of 22% (five of 23) in this cohort.[57] In addition, a modified humanized 14.18 (ie, hu14.18K322A) designed to blunt the complement activation thought to be responsible for neuropathic pain associated with GD2 immunotherapeutics demonstrated a 19% response rate in patients with disease detected only by MIBG scans.[58] Clinical trials evaluating anti-GD2 therapeutics and chemotherapy (irinotecan plus temozolomide; COG ANBL1221; ClinicalTrials.gov identifier NCT01767194) or the immunostimulatory molecule lenalidomide (NANT2011-04; ClinicalTrials.gov identifier NCT01711554) are under way. Additional pilot studies evaluating monoclonal antibody 1A7 as a surrogate GD2 vaccine[59] and active immunization against GD2 and GD3 combined with the immunostimulant β-glucan in patients with complete or very good partial remission have shown encouraging results.[60]

The remarkable remissions using autologous T cells engineered to express chimeric antigen receptors (CARs) in B-cell malignancies[61] have led to a growing interest in using CAR T cells for cellular-based therapy in neuroblastoma (Fig 3). Early trials of Epstein-Barr virus–specific cytotoxic T lymphocytes and activated T lymphocytes engineered to express GD2 CARs induced complete remissions in three (27%) of 11 patients with active disease, and CAR T cells were found to be persistent in the blood long after infusion.[62] A first-generation CAR T cell engineered to recognize the CE7 domain of L1-CAM, an adhesion molecule overexpressed on neuroblastomas, has undergone phase I testing,[63] and trials of second- and third-generation CAR T cells are under way.[64] Infusions of natural killer cells,[65] dendritic cells,[66] and allogeneic[67] or haploidentical[68] stem cells after myeloablative conditioning are under investigation, with the hypothesis that these cells will generate a graft-versus-tumor effect.

INTERNATIONAL NEUROBLASTOMA DATABASE

Members of the INRG Task Force recognized that the data collected on the large international cohort of patients with neuroblastoma to establish the INRG classification system would prove to be a valuable resource for the entire neuroblastoma research community. Importantly, cooperative groups have agreed to update follow-up data on patients currently included in the database and will add information on new patients enrolled onto clinical studies, once the primary results are published. A formal application process was developed to provide data to investigators for research studies, and to date, $>$ 20 projects have been conducted, including seminal studies never before possible with smaller patient cohorts. However, because of the limitations of the initial format of the INRG database, it was not possible to link the phenotypic data with the abundant genomic information that has been generated in laboratories around the world. To overcome this limitation, a live queryable database (interactive INRG database) was created in collaboration with the Center for Research Informatics at the University of Chicago, using technology that enables connections to other data sources.

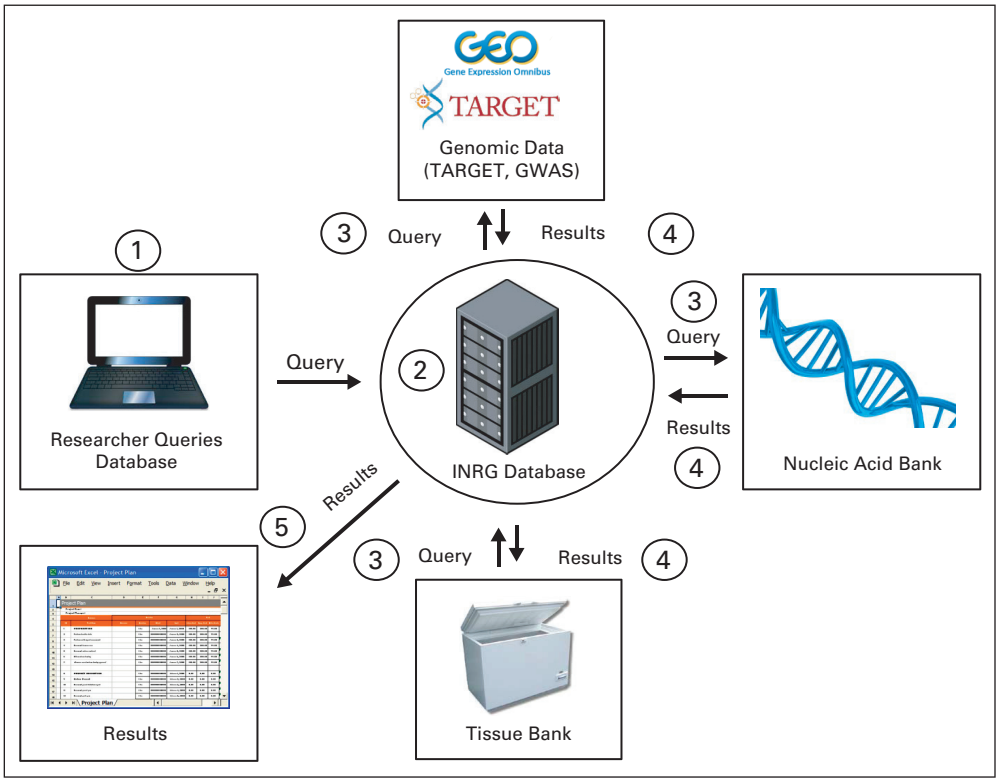

Fig 4. Workflow of interactive International Neuroblastoma Risk Group (INRG) database cohort discovery tool. (1) User builds query using interface. (2) Server executes query, returning cohort of patients to user. (3) Multiple affiliated data sources can be simultaneously queried. (4) Results are returned to server. (5) Aggregated results of query are presented back to researcher. GEO, Gene Expression Omnibus; GWAS, genome-wide association study; TARGET, Therapeutically Applicable Research to Generate Effective Treatments.

Connections with the COG Biobank and Nucleic Acids Bank have been established, and genomic data generated through the National Institutes of Health–sponsored Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program[69] have been catalogued in the interactive INRG database. Efforts to link array comparative genomic hybridization data[70] to the phenotypic data from patients enrolled onto the completed SIOPEN Infant Neuroblastoma European Studies are ongoing.[71] Connections to other tumor biobanks, genomic databases, and published data sets are planned for the near future, involving all contributing collaborative groups (SIOPEN, JNBSG, GPOH, and COG).

Investigators can now ask complex questions of the data and have instant access to aggregated data about sample availability using a public cohort discovery tool.[72] For example, a researcher can query the database to find out how many patients have nonmetastatic disease, *MYCN* amplification, and tissues samples stored in the COG Biobank and whether germline or tumor genomic data are available (Fig 4). The user could then use the query results to prepare a formal INRG research application to request more granular deidentified patient data and/or to build a neuroblastoma COG Biobank sample request. It is anticipated that by expanding the connections between the phenotype data in the interactive INRG database and genomic and biobank databases from around the world, landmark discoveries will ultimately translate into new treatment strategies and improved survival.

DISCUSSION

Collaborative efforts of institutions and international cooperative groups have led to significant progress in our understanding of neuroblastoma epidemiology and biology, refinements in risk classification, and advances in treatment strategies. Successive risk-based cooperative group clinical trials have led to decreased toxicity and improved outcome for low- and intermediate-risk patients, as well as higher survival rates for high-risk patients. In concert with this clinical research, international cooperative groups have collected large numbers of clinically annotated tumor and germline samples, and key somatic and germline genomic alterations have been discovered through the genomic interrogation of these samples. New paradigms relying on tumor and host molecular profiling are emerging to inform treatment decisions for children with neuroblastoma, although additional research is needed to clarify the genomic landscapes at presentation and relapse with greater accuracy. Furthermore, the paucity of identified actionable mutations in neuroblastoma tumors and limitations in the availability of drugs predicted to be beneficial remain significant challenges. To ultimately cure patients with high-risk neuroblastoma and improve their quality of life, we will need to change our long-held "more is better" approach and develop institutional and cooperative group clinical trials that incorporate precision treatment strategies based on specific tumor targets and pharmacogenomics. The neuroblastoma community has a long-standing history of working together. Further international collaborative effort will be required as therapeutic approaches designed to treat small subsets of genetically defined patients are developed.

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