

KIR and HLA Genotypes Are Associated with Disease Progression and Survival following Autologous Hematopoietic Stem Cell Transplantation for High-Risk NeuroblastomaJeffrey M. Venstrom,¹ Junting Zheng,² Nabila Noor,³ Karen E. Danis,⁴ Alice W. Yeh,³ Irene Y. Cheung,⁴ Bo Dupont,³ Richard J. O'Reilly,⁴ Nai-Kong V. Cheung,⁴ and Katharine C. Hsu¹

Abstract **Purpose:** NK cells exhibit cytotoxicity against neuroblastoma. Gene polymorphisms governing NK cell function, therefore, may influence prognosis. Two highly polymorphic genetic loci instrumental in determining NK cell responses encode the NK cell killer immunoglobulin-like receptors (KIR) and their class I human leukocyte antigen (HLA) ligands. We hypothesized that patients with a "missing ligand" *KIR-HLA* compound genotype may uniquely benefit from autologous hematopoietic stem cell transplantation (HSCT). **Experimental Design:** One hundred sixty-nine patients treated with autologous HSCT for stage IV neuroblastoma underwent *KIR* and *HLA* genotyping. Patients were segregated according to the presence or absence of HLA ligands for autologous inhibitory KIR. Univariate and multivariate analyses were done for overall and progression-free survival. **Results:** Sixty-four percent of patients lacked one or more HLA ligands for inhibitory KIR. Patients lacking a HLA ligand had a 46% lower risk of death [hazard ratio, 0.54; 95% confidence interval (95% CI), 0.35-0.85; $P = 0.007$] and a 34% lower risk of progression (hazard ratio, 0.66; 95% CI, 0.44-1.0; $P = 0.047$) at 3 years compared with patients who possessed all ligands for his/her inhibitory KIR. Among all *KIR-HLA* combinations, 16 patients lacking the HLA-C1 ligand for KIR2DL2/KIR2DL3 experienced the highest 3-year survival rate of 81% (95% CI, 64-100). Survival was more strongly associated with "missing ligand" than with tumor *MYCN* gene amplification. **Conclusion:** *KIR-HLA* immunogenetics represents a novel prognostic marker for patients undergoing autologous HSCT for high-risk neuroblastoma. (Clin Cancer Res 2009;15(23):7330-4)

Neuroblastoma is the most frequently diagnosed cancer in infants and is the most common extracranial solid tumor in childhood (1). Prognosis varies, and risk assessment is based on several clinical and biological features, including age, stage at diagnosis, histopathology, and biomarkers of tumor aggressiveness (*MYCN* status, histology, and DNA ploidy; refs. 2, 3). The risk of tumor progression likely depends

not only on tumor biology but also on the host immune response. NK cells are capable of inhibiting colony formation of human neuroblastoma cells (4-7), and infusion of NK cells into nonobese diabetic/severe combined immunodeficient mice bearing human metastatic neuroblastoma leads to a significant improvement in overall survival (4). Based on recent advances linking NK cell function to NK cell genetics (8-11), we hypothesized that variations in genes responsible for regulating NK function may affect clinical outcomes for patients with neuroblastoma.

The killer immunoglobulin-like receptor (*KIR*) gene cluster consists of 15 genes that encode both inhibitory and activating NK cell surface receptors instrumental in governing NK cell function. The similarly polymorphic human leukocyte antigen (*HLA*) class I gene loci encode three ligand groups for inhibitory KIR: *HLA* for KIR2DL2/KIR2DL3, *HLA* for KIR2DL1, and *HLA* for 12KIR3DL1. Ligation of inhibitory KIR by self-*HLA* class I ligands leads to NK inhibition (12). Moreover, NK cells expressing inhibitory KIR for self-*HLA* class I molecules are preferentially endowed with effector function, ensuring that potentially autoreactive NK cells expressing KIR for non-self *HLA* ("missing ligand") are rendered functionally incompetent when they encounter cells lacking their cognate ligand (13-16). Therefore, although ~60% of individuals have inhibitory KIR receptors for which they lack the *HLA* class I ligand ("missing

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Translational Relevance

There is a critical need for biomarkers for identifying patients likely to respond to hematopoietic stem cell transplantation (HSCT). For children with high-risk neuroblastoma, predicting outcomes following autologous HSCT would allow clinicians to individualize therapy, optimize long-term survival, and prevent unnecessary toxicities. In a population of neuroblastoma patients at high risk for relapse, we show that killer immunoglobulin-like receptor and human leukocyte antigen gene polymorphisms governing NK cell function influence disease progression and survival for patients treated with autologous HSCT. Combining prognostic markers linked to host innate immunity with markers of intrinsic tumor biology may more accurately model the host-tumor interaction and better predict survival. Our data open new possibilities for risk-stratifying neuroblastoma patients using a unique immune-based genetic algorithm and may have implications for other tumors treated with autologous HSCT.

ligand"; refs. 9, 17), their NK cells expressing KIR for non-self class I HLA molecules are hyporesponsive when encountering autologous tissue and incapable of effector function in the steady state (8, 13).

For patients with a *KIR-HLA* compound genotype predictive of "missing ligand," there is evidence that NK cells expressing inhibitory KIR for non-self HLA molecules are not rigidly hyporesponsive but may, in fact, become responsive and play a biologically important role. In settings of inflammation, such as infection or allogeneic hematopoietic stem cell transplantation (HSCT), normally hyporesponsive NK cells become cytotoxic to transformed tumor targets lacking the HLA class I ligand (8, 18, 19). Clinically, the "missing ligand" *KIR-HLA* compound genotype is associated with significantly improved outcomes for leukemia patients undergoing HSCT (20–23). We reasoned that comparable cytokine conditions may exist after high-dose chemotherapy with autologous HSCT, stimulating NK cells to behave according to "missing ligand." Through a retrospective analysis of *KIR* and *HLA* genotypes in high-risk neuroblastoma patients undergoing autologous HSCT, we show that patients with "missing ligand" *KIR-HLA* compound genotypes have improved outcomes and that *KIR-HLA* immunogenetics may provide a novel prognostic marker for high-risk neuroblastoma.

Materials and Methods

Patients. This is a retrospective analysis of 169 patients with stage IV neuroblastoma evaluated at Memorial Sloan-Kettering Cancer Center for immunotherapy following autologous HSCT between 1992 and 2007. Eighty-three patients were transplanted at Memorial Sloan-Kettering Cancer Center; 86 patients were transplanted at referring institutions. Patients completed five to seven cycles of induction chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, cisplatin, and etoposide (clinicaltrials.gov NCT00004188, NCT00002634, and NCT00040872; ref. 24). Autologous stem cells were harvested after two to three cycles

of induction therapy and cryopreserved. Patients with refractory disease after induction were treated with one to two additional cycles of cyclophosphamide, vincristine, topotecan, or irinotecan (25). The majority were transplanted in first response before disease progression with a preparative myeloablative regimen consisting of carboplatin, etoposide, melphalan or carboplatin, topotecan, and thiotepa (26–28). For local control, patients underwent total resection of the primary tumor followed by 2,100 cGy hyperfractionated radiotherapy (29). One hundred sixty-eight of 169 (99%) patients received immunotherapy with intravenous anti-ganglioside GD2 antibody 3F8. 3F8 was combined with subcutaneous granulocyte macrophage colony-stimulating factor in 59 patients (clinicaltrials.gov NCT00072358) and intravenous granulocyte macrophage colony-stimulating factor in 71 patients (clinicaltrials.gov NCT0002560). One hundred twenty-nine of 169 (76%) patients received oral isotretinoin. Investigators obtained informed consent for specimen collection and treatment from each participant or participant's guardian in accordance with local institutional review board guidelines.

HLA and KIR genotyping. Genomic DNA was extracted from peripheral blood mononuclear cells or bone marrow mononuclear cells using the QIAamp DNA minikit (Qiagen) according to the manufacturer's instructions. *HLA* alleles were identified by a combination of HLA serology, sequence-based amplification (PCR sequence-specific primer), and oligonucleotide probing of genomic DNA (PCR-specific oligonucleotide probe). *KIR* gene loci were typed as described previously (30). PCR sequence-specific primer was used to determine the presence or absence of inhibitory *KIR* genes (*KIR2DL1*, *KIR2DL2*, *KIR2DL3*, and *KIR3DL1*) and activating *KIR* genes (*KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1*).

KIR-HLA analysis. Patients were segregated according to the presence or absence of the HLA class I ligand for his/her inhibitory KIR. The algorithm considers the patient's inhibitory KIR (determined by *KIR* genotype) and the presence or absence of each cognate HLA class I ligand (determined by *HLA* genotype). HLA-A, HLA-B, and HLA-C molecules were placed into three groups (HLA-C1, HLA-C2, and

Table 1. Characteristics of neuroblastoma patients undergoing autologous HSCT ($n = 169$)

Characteristics	Patients, n (%)
Stage	
IV	169 (100)
Histology group	
Poor risk	102 (60)
Good risk	8 (5)
Unknown	59 (35)
Age, y	
<1.5	16 (9)
>1.5	153 (91)
<i>MYCN</i> amplification	
Yes	58 (35)
No	96 (57)
Unknown	15 (9)
Lactate dehydrogenase	
High	47 (28)
Low (<1,500 units/mol)	84 (50)
Unknown	38 (22)
Bone metastases	
Yes	131 (78)
No	38 (22)
<i>KIR-HLA</i> combinations	
All ligands present	61 (36)
Missing any ligand*	108 (64)

*Patients are scored "missing ligand" if the HLA ligand is absent and the patient possesses the *KIR* gene for the specific HLA ligand.

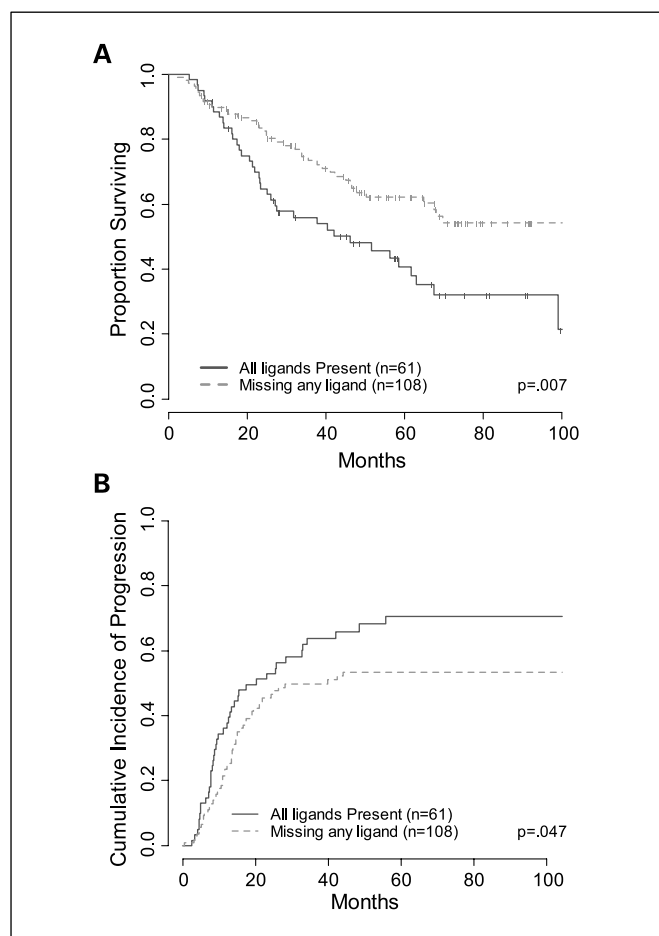


Fig. 1. Overall survival (A) and cumulative incidence of progression (B) following autologous HSCT in stage IV neuroblastoma patients with all ligands present or lacking one or more HLA class I ligand for inhibitory KIR.

HLA-Bw4) based on amino acid sequences determining the KIR-binding epitope. HLA-C allotypes with asparagine at position 80 (HLA-C1) are ligands for KIR2DL2 and KIR2DL3; HLA-C allotypes with lysine at position 80 (HLA-C2) are ligands for KIR2DL1; and HLA-A and HLA-B allotypes with the Bw4 epitope recognized by KIR3DL1 are distinguished by substitutions at positions 77, 80, 81, 82, and 83 in the carboxyl terminus of the HLA class I $\alpha 1$ domain (31–34).

Patients with “all ligands present” possess all HLA class I ligands for his/her individual inhibitory KIR genes. Patients lacking the HLA ligand for an identified inhibitory KIR were considered “missing ligand.”

Statistical analysis. Overall survival and progression-free survival were the primary and secondary endpoints, respectively. Overall survival was defined as the time from stem cell infusion to date of death, or last follow-up. Patients alive at the last follow-up were censored. Progression-free survival was defined from the date of stem cell infusion to the earliest date of progression or date of last follow-up. Patients alive without progression were censored. All patients who died experienced progression before death; therefore, death was not a competing risk for progression. Cumulative incidence rate of disease progression was calculated as 1 - progression free survival rate. The log-rank test was used to assess the effect of “missing ligand” on the outcomes. No adjustments were made for multiple comparisons. Hazard ratio (HR) estimates were based on Cox proportional hazards models. A multivariable Cox regression was used to assess the effect on overall survival of missing any HLA ligand, controlling for other clinical factors.

Results

Patient KIR and HLA relationships. Patient characteristics and KIR-HLA combinations are listed in Table 1. KIR genotyping of the 169 patients identified 95% of patients to be positive for KIR3DL1, 49% positive for KIR2DL2, 91% positive for KIR2DL3, and 98% positive for KIR2DL1. Sixty-four percent ($n = 108$) of patients lacked at least one HLA ligand for autologous inhibitory KIR. The gene frequencies and KIR-HLA relationships are representative of the Caucasian population and consistent with other studies (20, 30). Between patients missing at least one HLA class I ligand for inhibitory KIR and patients with all ligands present, there was no statistically significant difference for MYCN amplification, bone metastases, histology group, age, stage, or lactate dehydrogenase.

Missing ligand analysis. With a median follow-up of 67.4 months (range, 0.3–121 months) after autologous HSCT, the median survival for patients missing a HLA class I ligand was 9.5 years [95% confidence interval (95% CI) limit >5.7 years] compared with 3.8 years (95% CI, 2.3–5.7 years) for patients with all HLA class I ligands present ($P = 0.007$; Fig. 1A). Patients lacking a HLA class I ligand for autologous inhibitory KIR had a 46% lower risk of death compared with patients with all HLA ligands present (HR, 0.54; 95% CI, 0.35–0.85; $P = 0.007$). The 3-year cumulative incidence of progression was 64% (49–74%) for patients with all HLA class I ligands compared with 50% (39–59%) for patients lacking a HLA ligand (HR, 0.66; 95% CI, 0.44–1.0; $P = 0.047$; Fig. 1B). There was no treatment-related mortality in this cohort of patients; all patients who died had disease progression before death.

KIR and HLA specificity. To identify whether lack of a specific HLA class I ligand for an individual inhibitory KIR contributed more significantly to the overall survival advantage, patients were segregated into specific “missing ligand” groups. These groups were defined by the lack of either HLA-C1 for KIR2DL2/KIR2DL3, HLA-C2 for KIR2DL1, or HLA-Bw4 for KIR3DL1. Patients lacking the HLA-C1 ligand for KIR2DL2/KIR2DL3 ($n = 16$) had a 3-year survival rate of 81% (95% CI, 64–100), the highest of any subgroup, compared with 65% (95% CI, 58–74) for patients with HLA-C1 present (HR, 0.52; 95% CI, 0.21–1.30; $P = 0.155$), although this was not statistically significant. There was a similar trend for progression-free survival (HR, 0.52; 95% CI, 0.23–1.19; $P = 0.113$).

When we excluded the HLA-A Bw4 allotypes, we still identified a strong but more modest 14% increase in 3-year survival rate for patients missing any ligand (71% versus 57%; HR, 0.62; 95% CI, 0.39–0.98; $P = 0.041$) compared with a 17% increase in 3-year survival rate for patients missing any ligand when we included HLA-A Bw4 alleles (73% versus 56%; HR, 0.54; 95% CI, 0.35–0.85; $P = 0.007$).

In allogeneic HSCT, donor activating KIR and KIR haplotypes have also been associated with clinical outcomes (35). We therefore examined the influence of activating KIR on outcome. Patients were divided according to the presence or absence of activating KIR (2DS1, 2DS2, 2DS3, 2DS4, 2DS5, and 3DS1). There was no discernable effect of activating KIR on HSCT outcome (data not shown).

Other clinicopathologic and biological factors. To assess the effect of the “missing ligand” model relative to other known prognostic variables, univariate and multivariate analyses were done for patients with complete data for all reported clinical

Table 2. Clinicopathologic and biological factors associated with overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P*	HR (95% CI)	P [†]
Missing any ligand	0.54 (0.35-0.85)	<0.01	0.53 (0.32-0.88)	0.02
Age >1.5 vs <1.5 y	3.3 (1.04-10.51)	0.04	8.01 (1.10-58.60)	0.04
Bone marrow involvement	2.57 (0.94-7.04)	0.06	3.29 (0.78-13.84)	0.11
High lactate dehydrogenase >1,500 vs <1,500	1.81 (1.07-3.05)	0.02	2.09 (1.22-3.57)	0.01
Isotretinoin	0.47 (0.29-0.76)	<0.01	0.54 (0.31-0.94)	0.03
MYCN amplification	1.3 (0.81-2.11)	0.28	ND	
Poor-risk histology	4.41 (0.61-32.05)	0.12	ND	
Intravenous vs subcutaneous granulocyte macrophage colony-stimulating factor	1.15 (0.70-1.90)	0.59	ND	
HSCT regimen: TCT vs others	1.31 (0.81-2.12)	0.14	ND	
HSCT regimen: CEM vs others	0.71 (0.41-1.21)	0.14	ND	

Abbreviations: TCT, carboplatin, topotecan, thiotepa; CEM, carboplatin, etoposide, melphalan; ND, not determined.

*P determined by log-rank test.

[†]P determined by regression analysis.

covariates (Table 2). After adjusting for age, lactate dehydrogenase, isotretinoin, and bone marrow involvement, the effect of “missing ligand” in this subset of patients remained a significant factor associated with survival. MYCN amplification, poor-risk histology, HSCT regimen, and granulocyte macrophage colony-stimulating factor were not predictive of survival in univariate analyses (Table 2).

Discussion

Using a large and homogeneous cohort of neuroblastoma patients treated with autologous HSCT, we show a survival advantage in solid tumor patients lacking HLA class I ligands for autologous inhibitory KIR. Autologous HSCT may provide the milieu that promotes activation and expansion of NK cells leading to improved tumor control and survival following HSCT. This enhanced tumor immunity depends on the immunogenetic background of the patient, such that patients lacking the HLA class I ligand for autologous inhibitory KIR derive the greatest benefit from NK cell reactivity following HSCT. As a complement to current prognostic factors, KIR-HLA immunogenetics may provide useful insight into how innate immunity can be activated against neuroblastoma in HSCT.

These data support a model of NK cell behavior whereby tolerance to self is circumvented in autologous HSCT, allowing normally hyporesponsive NK cells expressing inhibitory KIR for non-self HLA class I molecules to achieve effector function and heightened eradication of tumor cells. Functional studies in murine cytomegalovirus infection and human allogeneic HSCT have recently confirmed NK reactivity according to “missing ligand” (9, 18, 19). The mechanism underlying this plasticity of NK cell tolerance remains obscure, but the inflammatory environment common to both viral infection and HSCT may be critical for breaking tolerance to self (18, 19). Similar functional studies in the autologous

HSCT setting are necessary, but early findings show that non-self-specific NK cells display functional competence following autologous HSCT in neuroblastoma patients.⁵ The finding that patients lacking the HLA-C1 ligand for KIR2DL2/KIR2DL3 had the highest 3-year survival rate is interesting when taken in the context of previous findings in the allogeneic HSCT setting where expression of KIR2DL2/KIR2DL3 is increased in the first 100 days post-HSCT (19). Similar phenotype-based reconstitution studies are needed in autologous HSCT.

Rapid and early NK cell recovery following autologous HSCT is associated with better progression-free survival in non-Hodgkin's lymphoma, Hodgkin's disease, acute myeloid leukemia, multiple myeloma, and metastatic breast cancer (36–38), indicating that other malignancies could potentially benefit from this “missing ligand” effect. In a heterogeneous cohort of 16 patients undergoing autologous HSCT for lymphoma and solid tumors, Leung et al. showed a survival advantage for recipients with a KIR-HLA mismatch (39), although another study had conflicting results (40). By restricting the analysis to a specific tumor population with sufficient numbers of patients, we can definitively show an innate immune effect dictated by inhibitory KIR-HLA interaction. Finally, other inflammatory stimuli or even other mechanisms of NK cell killing, such as antibody-dependent cellular cytotoxicity, may play a role, particularly because nearly all patients in this study received antibody therapy. A better understanding of the biological complexity responsible for the “missing ligand” effect is crucial for further exploiting NK cells in cancer therapy.

As a complement to known factors associated with neuroblastoma outcome including histology, DNA ploidy, MYCN gene amplification, and isotretinoin treatment (2, 3, 27), KIR-HLA immunogenetics may provide useful insight into how innate immunity can be activated against neuroblastoma in HSCT. In this study, “missing ligand” was more significant than tumor MYCN gene amplification. Isotretinoin also had a beneficial effect on survival, although isotretinoin treatment depended somewhat on disease status, which could not be completely adjusted for in the Cox regression analysis. Combining KIR-HLA genotyping with other markers of immune responsiveness, such as Fcγ receptor polymorphisms (41), may

⁵ Unpublished data.

ultimately allow clinicians to determine the most effective and least toxic treatment strategy for an individual patient.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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