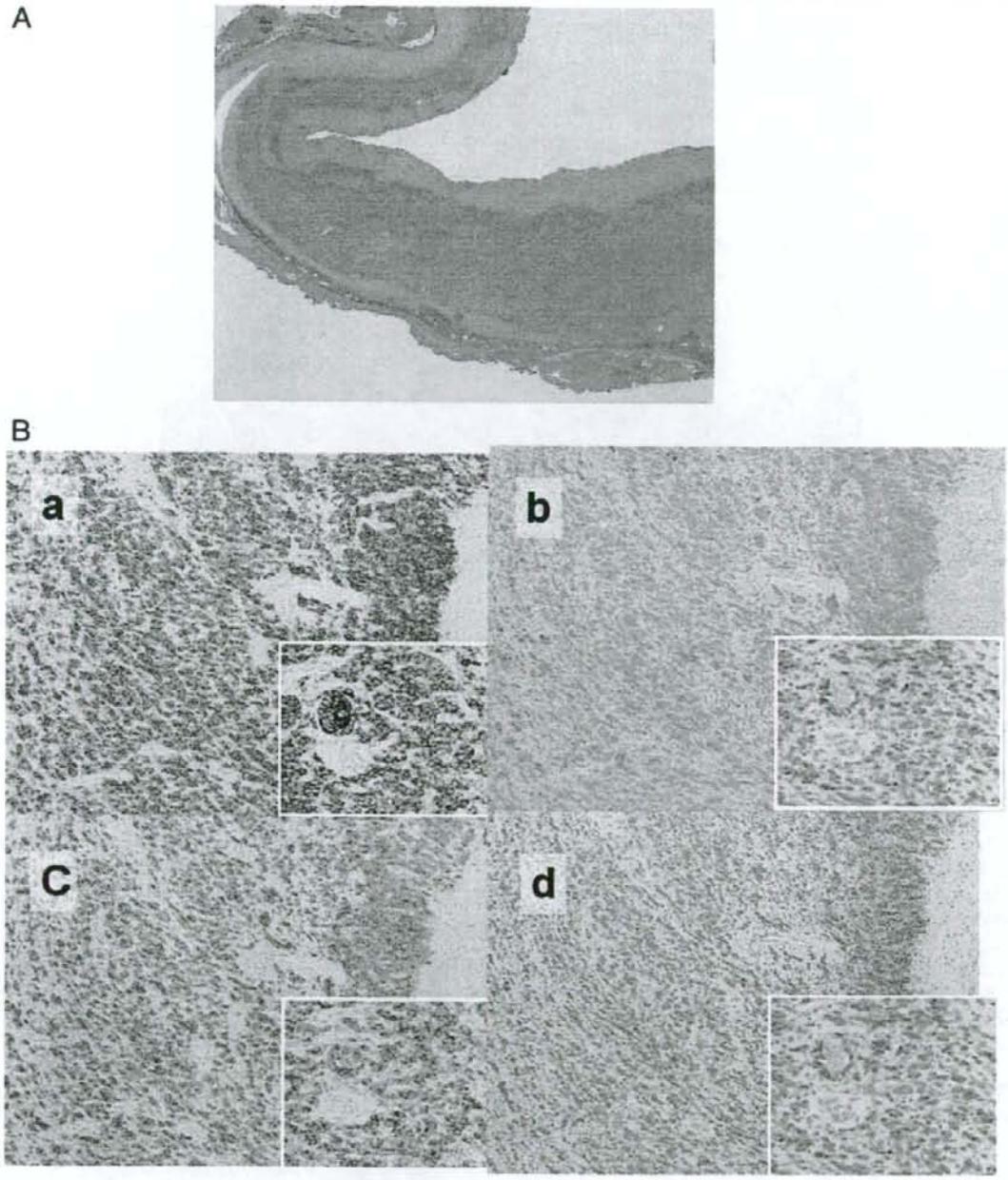

Fig. 3 A, Thick fibrous wall of the cystic lesion (H&E, × 20). Neuroblastic cells are densely packed in the wall circumferentially. B, Neuronal character of tumor cells confirmed by immunohistochemistry (a: CD56/NCAM × 100, left lower × 400; b: synaptophysin × 100, left lower × 400; c: chromogranin A × 100, left lower × 400; d: NSE × 100, left lower × 400). Tumor cells are positive for all these neuronal markers CD56/NCAM, synaptophysin, chromogranin A, and NSE (a, b, c, and d), whereas they are common leukocyte marker CD45-negative and epithelial marker pankeratin-negative. In addition, they are CD99/MIC2-negative.

chromogranin A, and NSE but negative for CD45 and pankeratin (Fig. 3B). Cells were also CD99/MIC2-negative. *MYCN* amplification was absent, and mitosis-karyorrhexis index was low. The final pathologic finding was CN with favorable histologic diagnosis. After the diagnosis had been determined, additional meta-iodobenzylguanidine scan and

urinary VMA, HVA were performed and found to be normal. Given this pathologic finding and negative metastatic workup, this tumor was determined to be treatable by surgery alone.

The patient received no further therapy and remains well as of 14 months after surgery. We have been following her with tumor markers, ultrasonographic and CT scan without any evidence of metastasis or tumor recurrence.

2. Discussion

Cystic neuroblastoma outside of the adrenal gland is an extremely unusual variant of neuroblastoma with a grossly visible cyst and almost always a distinctive microcyst [1,2,3]. Classically, pathologic finding of CN shows a grossly recognizable cyst lined by a thick fibrous wall with scattered clusters of neuroblastic cells, consistent with our case [1,2,3]. The tumor contained delicate neurofibrillary matrices; however, there was no microcyst. The tumor cells were immunohistochemically positive for neuronal markers such as CD56/NCAM, synaptophysin, chromogranin A, and NSE but were negative for CD45 and CD99/MIC2, both of which are characteristic of primitive neuroectodermal tumor. The pathologic diagnosis was poorly differentiated neuroblastoma, favorable histologic diagnosis.

Clinically, compared to solid neuroblastoma, CN is characterized by lower age of diagnosis, favorable stage, and favorable biology. Most cases of CN can be diagnosed prenatally [2,4]. Most CNs are located in the adrenal gland, and only 3 cases of extraadrenal CN have previously been described in the English literature, including two in the thorax and one in the presacral region [2,5].

The previously reported 2-month-old boy with a presacral CN had a very similar clinical course to the present case, including patient age, presenting symptoms, physical findings, laboratory findings, radiologic images, and clinical outcome [5]. Prenatal diagnosis was not made in either case. Both tumors contained a large amount of hemorrhagic fluid in the cyst.

Preoperative diagnosis of extraadrenal CN is quite difficult. Relatively common presacral cystic tumors in infants are teratoma, cystic lymphangioma, meningomyelocele, and chordoma. In the present case, CT and MRI identified a large, presacral, cystic tumor with septation [6]. The cystic wall of the tumor was very thin without any obvious solid component such as fat density or calcification. Although imaging studies were inconclusive, the most probable diagnosis given these findings is cystic teratoma or cystic lymphangioma. The presence of hemorrhage inside might have been more compatible with CN than with cystic teratoma. In addition to the rarity of presacral CN, lack of a massive solid component in the tumor made radiologic diagnosis more difficult. Urinary levels of VMA and HVA should have been examined, although most CNs reportedly show no elevation of those markers.

The authors emphasize that neuroblastoma should be considered as a possible diagnosis for infantile presacral tumor, even if the lesion is cystic.

References

[1] Atkinson Jr GO, Zaatari GS, Lorenzo RL, et al. Cystic neuroblastoma in infants: radiographic and pathologic features. AJR Am J Roentgenol 1986;146:113-7.

[2] Richards ML, Gundersen AE, Williams MS. Cystic neuroblastoma of infancy. J Pediatr Surg 1995;30:1354-7.

[3] Giulian BB, Chang CC, Yoss BS. Prenatal ultrasonographic diagnosis of fetal adrenal neuroblastoma. J Clin Ultrasound 1986;14:225-7.

[4] Petit T, de Lagausie P, El Ghoneimi A, et al. Postnatal management of cystic neuroblastoma. Eur J Pediatr Surg 2001;11:411-4.

[5] D'Alessio A, Piro E, Beretta F, et al. Presacral cystic neuroblastoma: case report and review of the literature. J Pediatr Hematol Oncol 2006; 28:534-6.

[6] Merten DF, Kirks DR. Diagnostic imaging of pediatric abdominal masses. Pediatr Clin North Am 1985;32:1397-425.

VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report

Tom Monclair, Garrett M. Brodeur, Peter F. Ambros, Hervé J. Brisse, Giovanni Cecchetto, Keith Holmes, Michio Kaneko, Wendy B. London, Katherine K. Matthay, Jed G. Nuchtern, Dietrich von Schweinitz, Thorsten Simon, Susan L. Cohn, and Andrew D.J. Pearson

From the Section for Paediatric Surgery, Division of Surgery, Rikshospitalet University Hospital, Oslo, Norway; Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA; Children's Cancer Research Institute, St Anna Kinderkrebsforschung, Vienna, Austria; Department of Radiology, Institut Curie, Paris, France; Pediatric Surgery-Department of Pediatrics, University of Padova, Padova, Italy; Department of Paediatric Surgery, St George's Hospital, London; Section of Paediatrics, Institute of Cancer Research and Royal Marsden Hospital, Surrey, United Kingdom; Department of Pediatric Surgery, University of Tsukuba, Tsukuba, Japan; Children's Oncology Group and Department of Epidemiology and Health Policy Research, University of Florida, Gainesville, FL; Department of Pediatrics, University of California School of Medicine, San Francisco, CA; Department of Pediatric Surgery, Texas Children's Hospital, Houston, TX; Department of Pediatric Surgery, Dr. von Hauner'sches Kinderspital, University of Munich, Munich; Department of Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Germany; and Department of Pediatrics, the University of Chicago, Chicago, IL.

Submitted February 18, 2008; accepted August 6, 2008; published online ahead of print at www.jco.org on December 1, 2008.

Supported by the William Guy Forbeck Research Foundation and Little Heroes Pediatric Cancer Research Fund; and Cancer Research UK and NHS funding to the NIHR Biomedical Research Centre (to A.D.J.P.).

Presented in part at the Advances in Neuroblastoma Research 12th Conference, May 17-20, 2006, Los Angeles, CA, and the International Society of Paediatric Oncology 38th Congress, September 18-21, 2006, Geneva, Switzerland.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Tom Monclair, MD, PhD, Section for Paediatric Surgery, Division of Surgery, Rikshospitalet University Hospital, NO-0027 Oslo, Norway; e-mail: tom.monclair@rikshospitalet.no.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2702-298/$20.00

DOI: 10.1200/JCO.2008.16.6876

ABSTRACT

Purpose

The International Neuroblastoma Risk Group (INRG) classification system was developed to establish a consensus approach for pretreatment risk stratification. Because the International Neuroblastoma Staging System (INSS) is a postsurgical staging system, a new clinical staging system was required for the INRG pretreatment risk classification system.

Methods

To stage patients before any treatment, the INRG Task Force, consisting of neuroblastoma experts from Australia/New Zealand, China, Europe, Japan, and North America, developed a new INRG staging system (INRGSS) based on clinical criteria and image-defined risk factors (IDRFs). To investigate the impact of IDRFs on outcome, survival analyses were performed on 661 European patients with INSS stages 1, 2, or 3 disease for whom IDRFs were known.

Results

In the INGRSS, locoregional tumors are staged L1 or L2 based on the absence or presence of one or more of 20 IDRFs, respectively. Metastatic tumors are defined as stage M, except for stage MS, in which metastases are confined to the skin, liver, and/or bone marrow in children younger than 18 months of age. Within the 661-patient cohort, IDRFs were present (ie, stage L2) in 21% of patients with stage 1, 45% of patients with stage 2, and 94% of patients with stage 3 disease. Patients with INRGSS stage L2 disease had significantly lower 5-year event-free survival than those with INRGSS stage L1 disease (78% ± 4% *v* 90% ± 3%; $P = .0010$).

Conclusion

Use of the new staging (INRGSS) and risk classification (INRG) of neuroblastoma will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world.

J Clin Oncol 27:298-303. © 2008 by American Society of Clinical Oncology

INTRODUCTION

The International Neuroblastoma Risk Group (INRG) classification system was developed to facilitate the comparison of risk-based clinical trials conducted in different regions of the world by defining homogenous pretreatment patient cohorts. As described in the companion article by Cohn and Pearson et al,[1] the INRG classification system was based on survival tree regression analyses of data collected on 8,800 patients. Because the International Neuroblastoma Staging System (INSS) stage of locoregional tumors is based on the degree of surgical resection, this staging system is not suitable for the INRG pretreatment risk classification system. Therefore, the INRG Task Force[1] (see Appendix, online only, for participants) developed a new staging system based on tumor imaging rather than extent of surgical resection.

The INSS was developed in 1986 after a meeting that was held to establish international consensus for a common staging system and response to therapy.[2,3] Although many countries around the world adopted the INSS, difficulties have been encountered. For example, according to the INSS, the same tumor can be either stage 1 or 3 depending on the extent of surgical excision, making direct comparison of clinical trials based on INSS stages difficult.[4] Furthermore, patients with localized disease who are observed because tumor regression is anticipated cannot be properly staged using INSS criteria.[5] An additional limitation of the INSS is that assessment of lymph node involvement is necessary for proper staging. However, lymph node sampling is subject to the

thoroughness of the individual surgeon, and the assessment of extra-regional lymph node involvement is difficult to apply uniformly.[2-4]

METHODS

Image-Defined Risk Factors

Since 1994, the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) has classified locoregional tumors as resectable or unresectable dependent on the absence or presence of "surgical risk factors," but independent of INSS stage.[6] Surgical risk factors are features detected on imaging that make safe, total tumor excision impracticable at the time of diagnosis.[6,7] The SIOPEN principle for stratifying patients with locoregional tumors by imaging features was adopted by the INRG Task Force at a conference in Whistler, Canada, in 2005, and used in the design of the INRG Staging System (INRGSS). However, to avoid confusion with the INSS, the terms resectable and unresectable are not used in the INRG system.

The premise is that a staging system based on preoperative, diagnostic images will be more robust and reproducible than one based on operative findings and approach. Furthermore, because digital radiographs can be reviewed centrally, the images can be evaluated uniformly. As the surgical risk factors are based on radiographic images, it was decided to use the term "image-defined risk factors" (IDRFs), and consensus was reached for the IDRFs listed in Table 1. The IDRFs and the INRGSS are designed for use at the time of diagnosis, but they may also be used at reassessments during treatment. Although not needed for staging patients with disseminated disease, it is recommended that the IDRF status of the primary tumor be recorded in all patients (including patients with metastatic disease), so that the impact of IDRFs on surgical resection, surgical complications, and outcome can be prospectively evaluated in all patients.

Table 1. Image-Defined Risk Factors in Neuroblastic Tumors

Ipsilateral tumor extension within two body compartments
Neck-chest, chest-abdomen, abdomen-pelvis
Neck
Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
Tumor extending to base of skull
Tumor compressing the trachea
Cervico-thoracic junction
Tumor encasing brachial plexus roots
Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
Tumor compressing the trachea
Thorax
Tumor encasing the aorta and/or major branches
Tumor compressing the trachea and/or principal bronchi
Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal
Tumor encasing the aorta and/or vena cava
Abdomen/pelvis
Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
Tumor encasing branches of the superior mesenteric artery at the mesenteric root
Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
Tumor invading one or both renal pedicles
Tumor encasing the aorta and/or vena cava
Tumor encasing the iliac vessels
Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that:
More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures
Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but *not* considered IDRFs
Multifocal primary tumors
Pleural effusion, with or without malignant cells
Ascites, with or without malignant cells

Abbreviation: IDRFs, image-defined risk factors.

Staging Investigations

Diagnosis. In the INRG classification system, the diagnosis of neuroblastoma will be made using INSS criteria.[3] A tissue diagnosis of neuroblastoma can be made by conventional histology (with or without immunohistology and increased urine or serum catecholamine or metabolites). A diagnosis can also be made if unequivocal tumor cells are seen in bone marrow samples and increased urine or serum catecholamines or metabolites are present.

Involvement of bone marrow. Bone marrow involvement should be assessed by two aspirates and two biopsies from bilateral sites according to the recommendations of the INSS.[3] Biopsy is not required for infants younger than 6 months of age. Bone marrow disease is determined by morphology on smears and biopsies. Biopsies should be complemented by immunohistochemical techniques. Immunocytologic and/or molecular techniques are also recommended to evaluate the presence of tumor cells in the bone marrow at the time of diagnosis, although the results of these assays are not used for staging (Beiske et al, manuscript in preparation on behalf of the INRG Task Force).

Required imaging studies. Computed tomography (CT) and/or magnetic resonance imaging (MRI) with three-dimensional measurements and of sufficient quality to address IDRFs is mandatory for imaging the primary tumor. The presence or absence of each individual IDRF should be evaluated and recorded (Table 1). When possible, metastatic sites should also be measured by CT and/or MRI, as this information may be needed to evaluate treatment response.

Iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy is mandatory, and it is recommended that the study is performed before tumor excision and according to the Standard Operating Procedure previously described.[8] One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. A single equivocal lesion on MIBG requires confirmation by another imaging modality (plain radiographs, and if negative, MRI) and/or biopsy.

Technetium-99 bone scintigraphy is required only exceptionally, but in all age groups, if MIBG positivity of the primary tumor cannot be confirmed (ie, the primary tumor is removed or is not MIBG-avid). An isolated bone uptake should be confirmed by another imaging modality and/or biopsy.

Staging Definitions

The short-version definitions of the four INRGSS stages are listed in Table 2.

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

Stage L1 tumors are localized tumors that do not involve vital structures as defined by the list of IDRFs (Table 1). The tumor must be confined within one body compartment, neck, chest, abdomen, or pelvis. The isolated finding of intraspinal tumor extension that does not fulfill the criteria for an IDRF (Table 1) is consistent with stage L1.

Stage L2 tumors are locoregional tumors with one or more IDRFs. The tumor may be ipsilaterally continuous within body compartments (ie, a left-sided abdominal tumor with left-sided chest involvement should be considered stage L2). However, a clearly left-sided abdominal tumor with right-sided chest (or vice versa) involvement is defined as metastatic disease.

Stage M is defined as distant metastatic disease (ie, not contiguous with the primary tumor) except as defined for MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumor with enlarged lower mediastinal nodes or a pelvic tumor with inguinal lymph node involvement is considered locoregional disease. Ascites and a pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumor.

Stage MS is metastatic disease in patients younger than 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow. Bone marrow involvement should be limited to less than 10% of total nucleated cells on smears or biopsy. MIBG scintigraphy must be negative in bone and bone marrow. Provided there is MIBG uptake in the primary tumor, bone scans are not required. The primary tumor can be L1 or L2 and there is no restriction regarding crossing or infiltration of the midline.

Special Conditions

In addition to the IDRFs, and independent of the patient's INRGSS stage, three special conditions should be recorded: multifocal primary tumors, pleural effusion, and ascites (Table 1). Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined above (ie, stage L1, L2, M, or MS).

Relationship of INSS and INRG Stage

The INSS system is not in keeping with the INRG goal of a pretreatment classification system because the INSS assessment is made after the completion of the initial surgical procedure, and the INSS assessment is strongly dependent on the approach of the individual surgeon. To address these limitations, the INRGSS was developed. However, the survival tree regression analysis that forms the basis for the INRG classification system[1] could not be performed in terms of INRGSS because the sample size of patients with known surgical risk factors (analogous to the IDRFs that define INRGSS) in the INRG database[1] (< 850) was too small relative to patients with known INSS stage (> 8,500). Posthoc statistical analyses were therefore performed to determine whether it was reasonable to assign staging in terms of IDRFs of INRGSS instead of INSS, and if the prognostic ability of clinical stage was preserved if INRGSS was used. The analyses were restricted to patients with INSS stages 1, 2, or 3 disease because by definition, INSS stage 4 is equivalent to INRGSS M, and INSS stage 4S is very similar to INRGSS MS. Simon et al[9] have previously demonstrated the prognostic value of using IDRFs to define stage in a retrospective review of German neuroblastoma studies. The only other available data that can be used to validate the clinical significance of IDRFs and the INRGSS are those from SIOPEN in the INRG database.[1] The posthoc analysis of the SIOPEN data was performed in an attempt to validate the findings of the German study.

Statistical Considerations

Cross-tabulation of INRGSS and INSS was performed. The primary analytic end point for the predictive ability of INRGSS was event-free survival (EFS). Time to event was defined as time from diagnosis until time of first occurrence of relapse, progression, secondary malignancy, or death, or until time of last contact if none of these occurred. Univariate analyses were performed to assess the prognostic ability of INRGSS. Kaplan-Meier curves were generated, and curves were compared using log-rank test, with P values less than .05 considered statistically significant.[10] EFS and overall survival (OS) values were reported at the 5-year time point ± SE (per Peto).[11] It was not the goal of this analysis to compare outcome for INRGSS versus INSS (as was done in the study of Simon et al[9]).

Table 3. Distribution of SIOPEN Patients by INRGSS Versus INSS

INSS Stage	INRGSS L1		INRGSS L2		
	No.	%	No.	%	Total No.
1	239	79	64	21	303
2	81	55	66	45	147
3	12	6	199	94	211
Total	332	50	329	50	661

Abbreviations: SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System.

RESULTS

A total of 661 patients with INSS stage 1, 2, and 3 disease from SIOPEN met INRG eligibility criteria and had known data for IDRFs. Twenty-one percent of patients with INSS stage 1, 45% of patients with INSS stage 2, and 94% of patients with INSS stage 3 disease had IDRFs (ie, in total, 50% of all localized tumors were INRGSS stage L2; Table 3). The remainder of patients who had no IDRFs were classified as having INRGSS stage L1 disease. Of the 661 SIOPEN patients, 474 patients had available outcome data. Both INSS and INRGSS were found to be highly prognostic. The EFS for patients with INRGSS stage L1 disease (90% ± 3%, n = 213) was statistically significantly higher than for stage L2 (78% ± 4%, n = 261; $P = .0010$; Fig 1). The OS for patients with INRGSS stage L1 disease (96% ± 2%) was also significantly higher than for patients with INRGSS stage L2 disease (89% ± 3%; $P = .0068$; Fig 2). The EFS for patients with INSS stage 1 disease (92% ± 3%, n = 209) was statistically significantly higher than for patients with INSS stage 2 (78% ± 6%, n = 103; $P = .0005$) and INSS stage 3 disease (75% ± 5%, n = 162; $P < .0001$), whereas patients with INSS stage 2 and 3 disease had similar EFS ($P = .6611$). The OS rates for patients with INSS stage 1, 2, and 3 disease were respectively 98% ± 2%, 95% ± 3%, and 84% ± 4%.

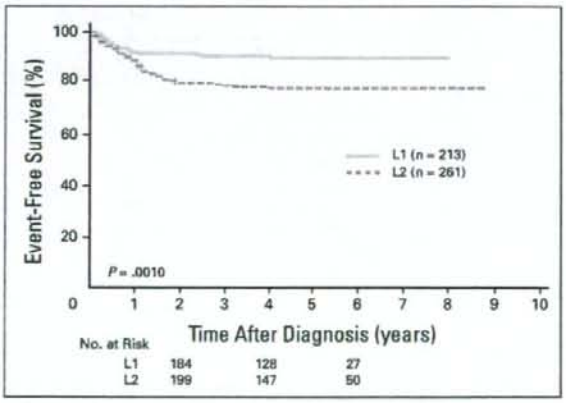

Fig 1. Event-free survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 ($P = .0010$; n = 474). The number of patients at risk for an event are shown along the curves at years 2, 4, and 6.

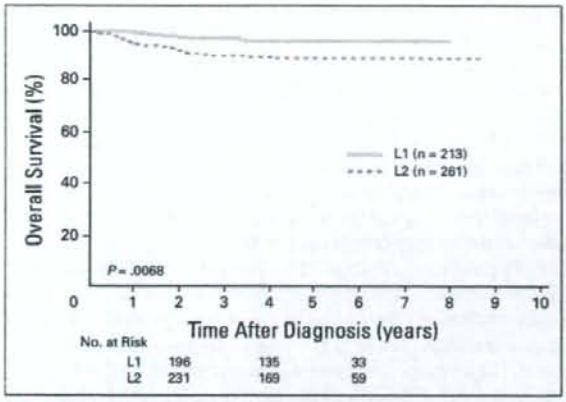

Fig 2. Overall survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 ($P = .0068$; n = 474). The number of patients at risk for death are shown along the curves at years 2, 4, and 6.

DISCUSSION

Because excision of the primary tumor is a prerequisite for assigning patients to INSS stages 1 and 2, and because it is possible to downstage patients by surgical treatment at diagnosis,[4] the INSS is not suitable for pretreatment staging and risk assessment. A new clinical staging system (INRGSS) was, therefore, designed specifically to constitute one of seven prognostic factors in the INRG pretreatment classification system.[1] In the INRGSS, locoregional disease is stratified into two stages instead of three (as in INSS). This decision was based on recognition of the increasing importance of biologic prognostic factors and the excellent OS rate for patients with nonmetastatic neuroblastomas.[1,12-16] Although the INRGSS can be used as a separate and independent clinical staging system, its primary function is as a component of the INRG. The INRGSS is not intended to substitute for the INSS, and it is anticipated that most cooperative groups will continue to use INSS in parallel with INRGSS.

Data from European studies show that absence or presence of IDRFs at diagnosis has prognostic significance. Our posthoc analysis of SIOPEN data[6] confirmed the results of Simon et al.[9] In both studies, EFS was lower for patients with INRGSS stage L2 compared with L1 tumors, and the differences were highly statistically significant. These observations support the translation of EFS tree regression results (in terms of INSS stages) into the INRG classification system (in terms of INRGSS): INSS 1 → INRGSS L1; INSS 2 and 3 → INRGSS L2; INSS 4 → INRGSS M; and INSS 4S → INRGSS MS.[1]

Because the treatment effect of tumor excision is an inherent part of the INSS, the prognostic value of specific stages within INRGSS and INSS cannot be directly compared. For example, most readers would agree that a comparison between patients with INRGSS stage L1 and INSS stage 1 is actually a comparison between an untreated group of patients and a cohort in whom nearly all patients have already been cured. However, even if INRGSS is not intended to substitute for the INSS, the distribution of patients between the two systems is of interest. In the retrospective study of Simon et al,[9] 84% of 160 patients with INSS stage 1 disease met the criteria for INRGSS stage L1 (ie, no IDRFs), whereas only 16% of 139 patients with IDRFs (stage L2) had INSS stage 1 disease. Similarly, our posthoc statistical analyses of 661 SIOPEN patients, in whom the clinical impact of surgical risk factors (= IDRFs) was examined prospectively, confirm the results of Simon et al.[9] In the data from SIOPEN (Table 3), 79% of patients with INSS stage 1 disease met the criteria for INRGSS stage L1, whereas 21% of patients with IDRFs (stage L2) had INSS stage 1 disease. In the SIOPEN LNESG1 study, 99% of 367 patients who met the criteria for INRGSS stage L1 underwent primary tumor excision (with one surgery-related death caused by renal failure). Among the 363 patients who underwent surgery, 75% had INSS stage 1 disease, 22% had INSS stage 2 disease, and 3% had INSS stage 3 disease. In 56% of 352 patients who had presence of one or more surgical risk factors (INRGSS stage L2), the initial surgical approach was limited to a biopsy; no attempt at primary tumor excision was made.[6] Furthermore, both studies referred to above demonstrated that primary operations in patients with IDRFs were associated with significantly lower complete excision rates and greater risks of surgery-related complications.[6,9]

Recommendations on treatment are not part of the INRGSS, nor of the INRG. Treatment policies must be decided by the individual cooperative groups. However, a new staging and risk classification system cannot exclude possible treatment alternatives, as is the case with INSS and the treatment option of observation without surgery. Today, OS in localized neuroblastoma is more than 90%,[1,12-16] and it can be assumed that a certain number of survivors have been overtreated. A main challenge in the years to come will be to maintain survival with reduced treatment. The INRGSS has been designed to permit uniform staging of all patients independent of the treatment alternatives contemplated.

The INRGSS differs from INSS in four important ways. First, it is based on preoperative imaging and IDRFs, not surgicopathologic findings. Second, the midline is not included in the staging criteria of the INRGSS. Third, lymph node status is not included in the staging of localized disease. Fourth, whereas INSS stage 4S has an upper age limit of 12 months, the Task Force decided to extend the age group for stage MS to patients younger than 18 months. The statistical basis for selecting a cutoff age of 18 months in INRG stages L2, M, and MS is presented and discussed in the companion article by Cohn and Pearson et al.[1] In one German study, the 5-year EFS was 100% in eight patients aged 12 to 18 months with *MYCN* nonamplified tumors who, apart from age, had classical INSS stage 4S disease.[17] The number of patients with "stage 4S disease aged 12 to 18 months" is small, but because the outcome in this patient cohort remains unclear, it is anticipated that the individual cooperative groups will give these patients special attention in prospective studies where careful stopping rules are included. Unlike INSS stage 4S, stage MS includes patients with primary tumors infiltrating the midline (INSS stage 3). The inclusion of all patients with stage L2 primaries is supported by the results of the SIOPEN 99.2 trial (B. De Bernardi, personal communication, February 2008). In this study, all 30 infants with INSS stage 4 disease having primary tumors corresponding to INSS stage 3 disease because of midline infiltration, and with stage 4S metastatic pattern, survived. Eight patients received no chemotherapy, and the remainder received only one or a few courses of chemotherapy to control symptoms. Only five of the patients had their primary tumor excised.

The effects of treatment on IDRFs are not known, although preliminary data from the SIOPEN Infant Neuroblastoma Study suggests that preoperative chemotherapy (or time) can decrease the incidence of IDRFs by 35% to 40%.[18] It also remains unclear whether the risks of surgical complications are reduced by preoperative chemotherapy when delayed operations are performed in patients who have persistent IDRFs. The impact of individual IDRFs on outcome is currently not known, and the clinical significance of individual IDRFs will need to be analyzed in a larger series of patients to address these questions.

Although surgery is not required for INRGSS staging, the biologic characteristics of the tumor must be known to stratify patients according to the INRG pretreatment classification system.[1] Image-guided core-needle biopsies are acceptable provided adequate material for the histologic and genetic studies are obtained. However, in many cases, complete or partial tumor excision may be a more rational way to obtain tissue for histologic categorization and genetic studies. In the latter case, it must be emphasized that the magnitude of the residual tumor does not influence the INRG stage. Even if completely excised at diagnosis, a localized tumor with (preoperative) one or more IDRFs will still be classified as an INRGSS stage L2.

The Task Force considered using a specific nomenclature to identify subgroups of patients with neuroblastoma with special features like multifocal primary tumors (because of the potential genetic implications of this diagnosis[19,20]). The experience with the INSS does not support a practice of subclassification within a staging system. Although the stage of patients with multifocal primary tumors in the INSS should be given a subscript letter M (stage 1_M, stage $2A_M$, and so on),[3] this subscript has not been widely accepted and only rarely used in published series. The Task Force, therefore, decided not to use subscripts in the INRGSS. This decision implies that patients with important special features not defined by the INRGSS have to be identified by other measures. It is recommended that data regarding the conditions listed in the last portion of Table 1 be collected.

Isolated pleural effusion and ascites are not considered IDRFs in the INRGSS. Although pleural disease is associated with reduced survival rates in patients with metastatic neuroblastoma,[21,22] isolated pleural effusion or ascites is rare in patients with locoregional disease, and its impact on outcome is not clear. In a recent study of 31 patients with neuroblastoma having pleural effusion, none had INSS stage 1 disease and only one had stage 2 disease.[23] It is assumed that the vast majority of patients with ascites also have either metastatic disease or the presence of IDRFs.

The extent of intraspinal tumor extension can range from a small tumor component bulging through one intervertebral foramen to a tumor occupying the majority of the spinal canal. In the SIOPEN studies, intraspinal tumor extension is considered a surgical risk factor if neurologic signs of spinal cord compression are present. However, because clinical signs are not image defined, in INRGSS, it was decided to consider intraspinal tumor extension an IDRF, provided one or more of the imaging criteria listed in Table 1 are present.

In conclusion, the INRGSS is a preoperative staging system that has been developed specifically for the INRG classification system. The extent of disease is determined by the presence or absence of IDRFs and/or metastatic tumor at the time of diagnosis, before any treatment. Use of this pretreatment staging system and the INRG classification system will facilitate the ability to compare results of risk-based clinical trials conducted in different regions of the world, and thereby, provide insight into optimal treatment strategies for patients with neuroblastic tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Tom Monclair, Garrett M. Brodeur, Peter F. Ambros, Hervé J. Brisse, Giovanni Cecchetto, Keith Holmes, Michio Kaneko, Wendy B. London, Katherine K. Matthay, Jed G. Nuchtern, Dietrich von Schweinitz, Susan L. Cohn, Andrew D.J. Pearson
Financial support: Wendy B. London, Susan L. Cohn
Administrative support: Susan L. Cohn, Andrew D.J. Pearson
Collection and assembly of data: Tom Monclair, Wendy B. London, Thorsten Simon, Susan L. Cohn, Andrew D.J. Pearson
Data analysis and interpretation: Tom Monclair, Garrett M. Brodeur, Keith Holmes, Wendy B. London, Katherine K. Matthay, Thorsten Simon, Susan L. Cohn, Andrew D.J. Pearson
Manuscript writing: Tom Monclair, Garrett M. Brodeur, Hervé J. Brisse, Giovanni Cecchetto, Keith Holmes, Wendy B. London, Katherine K. Matthay, Jed G. Nuchtern, Susan L. Cohn, Andrew D.J. Pearson
Final approval of manuscript: Tom Monclair, Garrett M. Brodeur, Peter F. Ambros, Hervé J. Brisse, Giovanni Cecchetto, Keith Holmes, Michio Kaneko, Wendy B. London, Katherine K. Matthay, Jed G. Nuchtern, Dietrich von Schweinitz, Thorsten Simon, Susan L. Cohn, Andrew D.J. Pearson

REFERENCES

1. Cohn SL, Pearson ADJ, London WB, et al: The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force report. J Clin Oncol [epub ahead of print on December 1, 2008]
2. Brodeur GM, Seeger RC, Barrett A, et al: International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. J Clin Oncol 6:1874-1881, 1988
3. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging and response to treatment. J Clin Oncol 11:1466-1477, 1993
4. Kushner BH, LaQuaglia MP, Kramer K, et al: Radically different treatment recommendations for newly diagnosed neuroblastoma: Pitfalls in assessment of risk. J Pediatr Hematol Oncol 26:35-39, 2004
5. Hero B, Simon T, Spitz R, et al: Localized infant neuroblastomas often show spontaneous regression: Results of the prospective trials NB95-S and NB97. J Clin Oncol 26:1504-1510, 2008
6. Cecchetto G, Mosseri V, De Bernardi B, et al: Surgical risk factors in primary surgery for localized neuroblastoma: The LNESG1 study of the European International Society of Pediatric Oncology Neuroblastoma Group. J Clin Oncol 23:8483-8489, 2005
7. Holmes K, Mosseri V, Cecchetto, et al: Surgical risk factors (SRF) and outcome following primary surgery for localised neuroblastoma: Results of LNESG1. Pediatr Blood Cancer 49:433, 2007 (abstr O. 127)
8. Olivier P, Colarinha P, Fettich J, et al: Guidelines for radioiodinated MIBG scintigraphy in children. Eur J Nucl Med Mol Imaging 30:B45-B50, 2003
9. Simon T, Hero B, Benz-Bohm G, et al: Review of image defined risk factors in localized neuroblastoma patients: Results of the GPOH NB97 trial. Pediatr Blood Cancer 50:965-969, 2008
10. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
11. Peto R, Peto J: Asymptotically efficient rank invariant test procedures. J Royal Stat Soc A 135: 185-198, 1972
12. Ikeda H, Iehara T, Tsuchida Y, et al: Experience with International Neuroblastoma Staging System and Pathology Classification. Br J Cancer 86: 1110-1116, 2002
13. Rubie H, Hartmann O, Michon J, et al: N-Myc gene amplification is a major prognostic factor in localized neuroblastoma: Results of the French NBL 90 study. J Clin Oncol 15:1171-1182, 1997

14. Perez CA, Matthay KK, Atkinson JB, et al: Biologic variables in the outcome of stages I and II neuroblastoma treated with surgery as primary therapy: A Children's Cancer Group study. J Clin Oncol 18:18-26, 2000

15. Evans AE, Silber JH, Shpilsky A, et al: Successful management of low-stage neuroblastoma without adjuvant therapies: A comparison of two decades, 1972 through 1981 and 1982 through 1992, in a single institution. J Clin Oncol 14:2504-2510, 1996

16. Matthay KK, Perez C, Seeger RC, et al: Successful treatment of stage III neuroblastoma based on prospective biologic staging: A Children's Cancer Group study. J Clin Oncol 16:1256-1264, 1998

17. Berthold F, Simon T, Mertens R, et al: Children with metastatic neuroblastoma between 12 and 18 months of age may represent "Biological stage 4S". Presented at the Advances in Neuroblastoma Research Conference, Los Angeles, CA, May 17-20, 2006 (abstr 298)

18. Squire R, Sarnacki S, Haider N, et al: The outcome of surgical procedures at diagnosis in localised infant neuroblastoma, and the effect of chemotherapy on resectability: European infant neuroblastoma study. Pediatr Blood Cancer 49:402, 2007 (abstr O. 011)

19. Maris JM, Kyemba SM, Rebbeck TR, et al: Molecular genetic analysis of familial neuroblastoma. Eur J Cancer 33:1923-1928, 1997

20. Hiyama E, Yokoyama T, Hiyama K, et al: Multifocal neuroblastoma: Biological behavior and surgical aspects. Cancer 88:1955-1963, 2000

21. Cowie F, Corbett R, Ross Pinkerton C: Lung involvement in neuroblastoma: Incidence and characteristics. Med Pediatr Oncol 28:429-432, 1997

22. Kammen BF, Matthay KK, Pacham P, et al: Pulmonary metastases at diagnosis of neuroblastoma in pediatric patients: CT findings and prognosis. AJR 176:755-759, 2001

23. Gupta H, Conrad J, Khoury JD, et al: Significance of pleural effusion in neuroblastoma. Pediatr Blood Cancer 49:906-908, 2007

Acknowledgment

INRG Task Force members: Susan L. Cohn, Andrew D.J. Pearson, Wendy B. London, Emanuele S.G. d'Amore, Andreas Faldum, Barbara Hero, Tomoko Iehara, David Machin, Veronique Mosseri, Michel Peuchmaur, Hiroyuki Shimada, Peter F. Ambros, Inge M. Ambros, Garrett M. Brodeur, Jerome Couturier, Michelle Haber, Javed Khan, John M. Maris, Akira Nakagawara, Gudrun Schleiermacher, Frank Speleman, Ruediger Spitz, Nadine Van Roy, Katherine K. Matthay, Klaus Beiske, Sue Burchill, Irene Cheung, Francesco Giammarile, Eiso Hiyama, Jean Michon, Robert C. Seeger, Barry Shulkin, Tom Monclair, Hervé Brisse, Giovanni Cecchetto, Keith S.J. Holmes, Michio Kaneko, Jed G. Nuchtern, Dietrich von Schweinitz, Frank Berthold, Victoria Castel, Robert P. Castleberry, Nai-Kong Cheung, Bruno De Bernardi, Helen Irving, Ruth Ladenstein, C. Patrick Reynolds, Jinhua Zhang, Julie R. Park, Roswitha Schumacher-Kuckelkorn, Thorsten Simon, Hidetaka Niizuma, Toby Trahair, Jennifer Forbeck, and John T. Kemshead. Participants in the INRG Meeting (September 17-19, 2005, Whistler, Vancouver, British Columbia, Canada), locations and group names, and roles are listed in Appendix Table A1, online only.

Pediatrics International (2008) **50**, 235–237 doi: 10.1111/j.1442-200X.2008.02544.x

Patient Report

Hypercalcemia induced by 13 cis-retinoic acid in patients with neuroblastoma

Hideo Mugishima, Motoaki Chin, Miyako Suga, Hiroyuki Schichino, Naohiro Ryo, Masanori Nakamura and Kensuke Harada

Department of Pediatrics, Division of Cell Regeneration and Transplantation, Advanced Medical Research Center, Nihon University School of Medicine, Tokyo, Japan

Key words 13 cis-retinoic acid, hypercalcemia, neuroblastoma.

Retinoic acid (RA) has been shown to induce differentiation, inhibit proliferation, and decrease the expression of the *MYCN* oncogene in neuroblastoma cell lines *in vitro*.[1] A trial of 13-cis-retinoic acid (cis-RA) for progressive neuroblastoma that is refractory to chemotherapy found few responses.[2] cis-RA may be effective in preventing relapse from minimal residual disease remaining in neuroblastoma patients after bone marrow transplantation (BMT).[3] In addition, cis-RA is likely to be well-tolerated after transplantation because its clinical toxicities have been mild and limited primarily to cheilitis, dry skin, conjunctivitis, and hypertriglyceridemia.[4] Hypercalcemia has not been previously reported as a dose-limiting toxicity for this agent, although it has been well documented in excessive intake of vitamin A.

In the present study we report on two patients who developed significant hypercalcemia while receiving oral cis-RA. The serum calcium levels should be closely monitored in patients with renal insufficiency who receive 13 cis-RA.

Case reports

Patient 1

A 7-year-old girl with a left peritoneal mass was diagnosed with stage 3 neuroblastoma when she was 1 year and 11 months old. The tumor was incompletely removed after she received a short course of combined chemotherapy consisting of vincristine, cyclophosphamide and doxorubicin. The patient had relapse at the primary site during chemotherapy. The patient received marrow-ablative chemotherapy consisting of cisplatin, etoposide, doxorubicin and melphalan, followed by autologous bone marrow transplantation (A-BMT).

Correspondence: Hideo Mugishima, MD, PhD, Department of Pediatrics, Nihon University School of Medicine, 30-1, Ooyaguchi-kami-machi, Itabashi-ku, Tokyo, 173-8610, Japan. Email: mugishim@med.nihon-u.ac.jp

Received 5 October 2005; revised 21 February 2006; accepted 2 April 2006.

The primary tumor mass was enlarged 1 year after A-BMT. She was transferred to Nihon University Itabashi Hospital for reinduction chemotherapy, tumor removal and intraoperative irradiation. Hematological recovery after transplant, however, was very poor and a high dose of cis-RA 400 mg/m^2 (120 mg orally twice/day) was given for 1 day with her parent's consent. At that time the patient's baseline calcium level was 8.0 mg/dL (normal 8.4–10.2 mg/dL), albumin level was 3.9 mg/dL (normal 3.5–4.8 mg/dL), and creatinine clearance was 62 mL/min per 1.73 m^2. Vanillactic acid (VMA) (normal <15 μg/mgCr) and homovanillic acid (HVA) (normal <26 μg/mgCr) were 35.0 μg/mgCr and 26.1 μg/mgCr, respectively. On day 3 of cis-RA therapy the patient complained of headache and hypertension (140/80 mmHg). On day 5 she started vomiting and had convulsion due to hypertension (170/110 mmHg).

This symptom was controlled by the oral administration of nifedipine 0.5 mg/day. On day 7 the patient complained of peeling skin around the mouth, abdominal discomfort, and arthralgia. Her serum calcium level was 8.2 mg/dL. On day 12 the levels of VMA and HVA (14.2 μg/mgCr and 16.5 μg/mgCr) decreased to the respective normal ranges. At that time the calcium level was 8.8 mg/dL and creatinine clearance was 26.8 mL/min per 1.73 m^2.

On day 18 a 7 day course of cis-RA was started at approximately 1/10 the initial dose: 13 cis-RA 40 mg/m^2 per day (10 mg capsule orally twice/day). After a 7 day course of treatment, severe skin-peeling was noted, the calcium level was 9.0 mg/dL, the albumin level was 3.6 mg/dL, and creatinine clearance was 29.8 mL/min per 1.73 m^2. Five days after the 7 day course of treatment, the concentration of cis-RA was 4.33 μmol/L on high-performance liquid chromatography (HPLC), which was significantly high. Nine days after the 7 day course of treatment, the calcium level was elevated to 16.8 mg/dL, the alkaline phosphatase level was 568 U/L (normal 117–335 U/L), and the triglyceride level was 260 mg/dL (normal 55–150 mg/dL). The patient received hydration with normal saline followed by i.v. furosemide. One week later the levels of calcium (8.2 mg/dL), alkaline phosphatase, (320 U/L) and triglyceride (145 mg/L) were within the respective normal ranges, and the patient complained of no symptoms other than a skin rash. At that time, creatinine clearance was 57.5 mL/min per 1.73 m^2.

Patient 2

A 3-year-old boy with a left adrenal mass was diagnosed with stage 4 (*MYCN* 150 copies) neuroblastoma when he was 2 years and 11 months old. The patient received five courses of a 98A3 regimen consisting of vincristine, cyclophosphamide, doxorubicin and cisplatin.[5] The tumor and left kidney were completely removed and 10 Gy intraoperative irradiation was applied after he received marrow-ablative chemotherapy consisting of cisplatin, etoposide, doxorubicin and melphalan, followed by A-BMT.

Three months after removal of the tumor and intraoperative irradiation, cis-RA 130 mg/m^2 per day was started for 2 weeks, followed by a 2 week rest period, and this was repeated for six cycles over a 24 week period. On day 12 of the first 2 week cycle, he was hospitalized for fungal pneumonia and was given fluconazole at 90 mg/day i.v. for 13 days and then at 100 mg/day orally for 14 days. On day 5 of the second 2 week cycle, when he was discharged, his calcium level was 9.9 mg/dL, blood urea nitrogen was 22.9 mg/dL, and serum creatinine was 0.63 mg/dL.

When he visited the outpatient clinic on day 9 of the second 2 week cycle his calcium level was 17.0 mg/dL, parathyroid hormone (PTH) was 5 pg/mL (normal 10–65 pg/mL), parathyroid related protein was 1.1 pmol/L (normal >1.1 pmol/L), blood urea nitrogen was 43.3 mg/dL, serum creatinine was 1.18 mg/dL, and creatinine clearance was 27.2 mL/min per 1.73 m^2. He was hospitalized for the episode of hypercalcemia without any clinical symptoms. During this hospitalization, cis-RA and fluconazole were stopped entirely. The patient received hydration with normal saline, followed by i.v. furosemide and hydrocortisone. At 5 days after stopping the cis-RA and fluconazole, his calcium level was 8.5 mg/dL, blood urea nitrogen was 24.7 mg/dL, and serum creatinine was 0.70 mg/dL. After the third 2 week cycle without fluconazole, his calcium level ranged from 8.9 to 10.6 mg/dL, blood urea nitrogen ranged from 24.8 to 29.8 mg/dL, and serum creatinine ranged from 0.61 to 0.86 mg/dL. The concentration of cis-RA was not measured in this patient. His serum calcium remained normal.

Discussion

Retinoids, which are vitamin A derivatives, are known to cause hypercalcemia.[6] Retinoic acid may regulate bone cell proliferation and differentiation by suppressing alkaline phosphatase activity, osteocalcin production, and prostaglandin-induced interleukin-6 synthesis in osteoblast cells.[7] The synthetic retinoid 13-cis-RA, or isotretinoin, has been shown to regulate cell proliferation and differentiation and to decrease *MYCN* expression.[1] Hypercalcemia has been reported in patients with neuroblastoma who are receiving 13-cis-RA.[6] Villablanca *et al.* reported a phase I trial of this drug in children with neuroblastoma after BMT that examined the toxicities, pharmacokinetics, and maximum tolerated dosage.[8] The 51 patients between 2 and 12 years of age received cis-RA in two equal doses daily for 2 weeks, followed by a 2 week rest period, for up to 12 courses. The dose was escalated from 100 to 200 mg/m^2 per day until dose-limiting toxicity was observed. Three patients developed grade 4 hypercalcemia, one at 160 mg/m^2 per day and two at 200 mg/m^2 per day, and one patient developed grade 3 hypercalcemia at 200 mg/m^2 per day. Only one of these patients was asymptomatic, and had both myalgias and arthralgias. They concluded that hypercalcemia may be a dosage-limiting adverse effect of 13-cis-RA. Accordingly, they advised that serum calcium levels should be monitored in patients receiving high dosages of this drug.[6]

Patient 1 received a high dose of cis-RA (400 mg/m^2 per day) and developed very severe acute clinical toxicities of cis-RA, including headache, vomiting, hypertension, convulsion and arthralgia. These were considered to be symptoms of pseudotumor cerebri. The pseudotumor cerebri is very rare with 13-cis RA. While these symptoms were present, the serum level of calcium was within the normal range. It is likely that neither the severity of clinical symptoms nor the dose of cis-RA correlates with the serum level of calcium. Twelve days after the administration of a high dose of cis-RA, the patient developed renal insufficiency, with creatinine clearance of 26.8 mL/min per 1.73 m^2. A high dose of cis-RA may affect renal function.

Eighteen days after the administration of a high dose of cis-RA, the patient received approximately 1/10 the initial dose: to 40 mg/m^2 per day for 7 days and developed severe skin toxicity. Nine days after this 7 day course of treatment the serum calcium level was elevated to 16.8 mg/dL, along with the alkaline phosphatase and triglyceride levels. Four days before the peak level of calcium, the concentration of cis-RA was 4.33 μmol/L on HPLC. If the concentration of cis-RA had been measured at the peak level of calcium, it may have been much higher. But in patients in a phase I study, no correlation was found between hypercalcemia and peak plasma levels of cis-RA.[8] In that study, pharmacokinetic data were available for only five patients. Data from a greater number of patients will be needed to confirm that this toxicity is not related to peak plasma levels.

Patient 2, who experienced hypercalcemia (serum calcium 17.0 mg/dL), was asymptomatic and had been receiving 13-cis-RA at 130 mg/m^2 per day. Belden and Ragucci demonstrated that hypercalcemia may be a dosage-limiting adverse effect of 13-cis-RA in children receiving an initial dosage of 160 mg/m^2 per day.[9] This dose is not likely to develop either clinical toxicity or episodes of hypercalcemia, but patient 2 developed hypercalcemia. In this patient a low level of PTH was measured at the time of hypercalcemia. It has been reported that RA can inhibit PTH, which suggests that increased bone resorption may account for hypercalcemia.[7]

Before developing hypercalcemia patient 2 had received fluconazole for the treatment of fungal pneumonia, and had renal insufficiency. The cause of hypercalcemia in this patient, who received cis-RA at 130 mg/m^2 per day, may have been renal insufficiency associated with the antifungal drug fluconazole and hemi-kidney. Two other patients who were reported to have severe hypercalcemia at this initial dosage of 160 mg/m^2 per day had renal insufficiency.[6,9] Their hypercalcemia resolved with hydration, diuretic therapy, and temporary discontinuation of 13-cis-RA. In conclusion, the present findings support previous evidence that hypercalcemia is a dosage-limiting adverse effect of 13-cis-RA therapy in patients with neuroblastoma. But hypercalcemia with 13-cis-RA at 130 mg/m^2 per day can occur if the

patient has renal insufficiency. Therefore, serum calcium levels should be closely monitored in patients with renal insufficiency who receive 13-cis-RA.

References

1 Thiele CJ, Reynolds CP, Israel MA. Decreased expression of N-myc precedes retinoic acid-induced morphological differentiation of human neuroblastoma. *Nature* 1985; **313**: 404–6.

2 Finkelstein JZ, Lenarsky C, Ladisch S *et al.* 13-cis-retinoic acid (NSC 122758) in the treatment of children with metastatic neuroblastoma unresponsive to conventional chemotherapy: report from the Children's Cancer Study Group. *Med. Pediatr. Oncol.* 1992; **20**: 307–11.

3 Marthay KK, Villablanca JQ, Seeger RC *et al.* Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *N. Engl. J. Med.* 1999; **341**: 1165–73.

4 Olson JA. Adverse effects of large doses of vitamin A and retinoids. *Semin. Oncol.* 1983; **10**: 290–93.

5 Kaneko M, Tsuchida Y, Mugishima H *et al.* Intensified chemotherapy increases the survival rate in patients with stage 4 neuroblastoma with MYCN amplification. *J. Pediatr Hematol Oncol.* 2002; **24**: 613–21.

6 Villablanca JG, Khan AA, Avramis VI *et al.* Hypercalcemia: A dose limiting toxicity associated with 13-cis-retinoic acid. *Am. J. Pediatr. Hematol. Oncol.* 1993; **15**: 410–15.

7 Ahmed N, Sammons J, Khokher A *et al.* Retinoic acid suppresses interleukin 6 production in normal human osteoblasts. *Cytokine* 2000; **12**: 289–93.

8 Villablanca JG, Khan AA, Avramis VI *et al.* Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation. *J. Clin. Oncol.* 1995; **13**: 894–901.

9 Belden TL, Ragucci DP. Hypercalcemia induced by 13-cis-retinoic acid in a patient with neuroblastoma. *Pharmacotherapy* 2002; **22**: 645–8.

CURRENT TOPICS

小児腫瘍のグループスタディーと病理

藤本純一郎[*1]　堀江　弘[*2]

はじめに

今から約6年前に各種難治性疾患に関わるエビデンス創出の基盤づくりのための公的研究費投入が開始された．それを受けて，小児がんについても標準的治療法開発を目指した取り組みが開始された．現在，我が国では小児がんの病型ごとの臨床研究グループがつくられ，統一治療プロトコールに基づく臨床試験などが実施されている．各研究グループには数十～200程度の医療施設が参加している．それらの組織体制は種々であるが，運営委員会や幹事会等の運営母体，プロトコール作成や研究立案を行う各種委員会，研究事務局，データセンター，中央診断システム等から構成されている．

上記の組織体制の中で，病理医が関与する場は主として中央診断システムの部分である．その他，臨床研究グループにおける中央診断に関わる業務は様々で，病理診断以外に，遺伝子診断（増幅，欠失，変異，キメラ遺伝子発現等），染色体診断，骨髄スメア等の形態診断，CT・MRI等画像診断，などが存在する．中央診断システムの役割は標準化された診断による試験参加適格性判定や治療層別化判定に関連する情報提供が基本であるが，一部では治療層別化に有用な新規マーカー開発研究や病態解明に結びつく基礎研究も行われる場合がある．病理中央診断については日本病理学会小児腫瘍組織分類委員会の委員の多くが関わってきた．

小児がんは稀少であり，年間の発生数が1,500～2,000程度と予想されることから，これらの症例を効率よく収集するシステムとしても臨床研究グループによる症例のリクルート，その中での中央診断システムは貴重である．また，診断後の余剰検体や研究用検体を保存し，基礎研究の推進に活用する仕組みも確立中である．また，小児がんの年間発生数把握に関する取り組みも始まっている．我が国におけるがん登録に対する取り組みは甚だしく遅れており，小児がん登録についても言わずもがなの状況である．しかしながら上記の臨床研究の推進ならびに予後の著明な改善に伴い，小児がん登録の重要性が増している．

本稿ではこれらの取り組みの現状を紹介する．

Ⅰ．小児がん臨床研究グループの活動

小児がんを扱う我が国の臨床研究グループとして専門家の間で認知されているものは**表1**に示した7つである．この中で日本小児白血病・リンパ腫研究グループ（JPLSG）が最も規模が大きい．小児血液腫瘍のプロトコールスタディを実施していた既存の4つの臨床研究グループ（CCLSG，JACLS，KYCCSGおよびTCCSG）がインターグループとして結集して形成されたもので，我が国の主たる小児がん治療施設のほとんどが参加している．小児血液腫瘍および血液系関連疾患に対する臨床試験11件を現在実施している（**表2**）．JPLSGのホームページでの組織図によると，代議員会と運営委員会が運営の中心となっており，その周囲に各種委員会，データセンター，検体センター等が配置されている．血液腫瘍以外の小児固形腫瘍については，基本的には病型ごとに研究グループが形成されている．小児の代表的な固形腫瘍である神経芽腫，横紋筋肉腫，Ewing肉腫，Wilms腫，肝芽腫については，それぞれ，JNBSG，JRSG，JESS，JWiTS，JPLTのグループが形成されている．なお，小児脳腫瘍についてはJPBTCというNPOとして活動している．また，多くの研究グループは何らかの形で公的研究費の支援を受けながら活動している．治療介入型の臨床試験を実施しているグループが大半だが，ガイドライン治療を実施し基盤となる情報収集を目的とした観察研究に近い形の研究もある．

[*1]国立成育医療センター研究所
[*2]千葉県こども病院検査部病理科

0287-3745/08/¥100/頁/JCLS

表1　我が国の主要な小児がん臨床研究グループ

小児がん臨床研究グループ名	対象病型	実施中の試験数	ホームページなどの情報
日本小児白血病・リンパ腫研究グループ（JPLSG）	白血病，悪性リンパ腫など	11	http://jplsg.jp
日本横紋筋肉腫研究グループ（JRSG）	横紋筋肉腫	4	文献1
日本ユーイング肉腫研究グループ（JESS）	Ewing肉腫	1	文献2
日本神経芽腫研究グループ（JNBSG）	神経芽腫	2	http://www.jnbsg.jp/
日本小児肝癌スタディグループ（JPLT）	肝芽腫など	1	http://home.hiroshima-u.ac.jp/jpltstudy/index.html
日本ウィルムス腫瘍スタディグループ（JWiTS）	Wilms腫	1	文献3
日本小児脳腫瘍コンソーシアム（JPBTC）	髄芽腫など	2	http://www.es-bureau.org/contents/consortium/

表2　現在進行中の小児がん関連臨床試験一覧

病型	試験名	研究グループ	試験ID*
急性リンパ性白血病	・乳児急性リンパ性白血病に対する早期同種造血幹細胞移植療法の有効性に関する後期第II相試験（MLL03）	JPLSG	
	・小児フィラデルフィア染色体陽性急性リンパ性白血病（Ph＋ALL）に対するimatinib mesylate第II相臨床試験（Ph＋ALL04）	JPLSG	C000000290
急性骨髄性白血病	・小児急性前骨髄急性白血病（APL）に対する多施設共同後期第II相臨床試験（AML-P05）	JPLSG	UMIN000000645
	・小児急性骨髄性白血病（AML）に対する多施設共同後期第II相臨床試験（AML-05）	JPLSG	UMIN000000511
	・ダウン症候群に発症した小児急性骨髄性白血病に対するリスク別多剤併用化学療法の後期第II相臨床試験（AML-D05）	JPLSG	UMIN000000989
悪性リンパ腫	・ALCL99（未分化大細胞型リンパ腫を対象としたヨーロッパとの共同研究）	JPLSG	
	・小児成熟B細胞性腫瘍に対する多施設共同後期第II相臨床試験（B-NHL03）	JPLSG	C000000317
	・進行期小児成熟B細胞性腫瘍に対する顆粒球コロニー刺激因子（G-CSF）の一次的予防投与の有用性に関する無作為割付比較試験（B-NHL03 G-CSF）	JPLSG	UMIN000000675
	・小児リンパ芽球型リンパ腫stage I/IIに対する多施設共同後期第II相臨床試験（LLB-NHL03）	JPLSG	
	・小児リンパ芽球型リンパ腫stage III/IVに対する多施設共同後期第II相臨床試験（ALB-NHL03）	JPLSG	
血球貪食症候群	・Treatment Protocol of the Second International HLH Study（HLH-2004）	JPLSG	
横紋筋肉腫	・横紋筋肉腫低リスクA群患者に対する短期間VAC 1.2療法の有効性および安全性の評価第II相臨床試験	JRSG	
	・横紋筋肉腫低リスクB群患者に対する短期間VAC 2.2/VA療法の有効性および安全性の評価第II相臨床試験	JRSG	
	・横紋筋肉腫中間リスク群に対するiVAC療法の有効性および安全性に関する多施設共同研究	JRSG	
	・進行性・転移性横紋筋肉腫に対する自家造血幹細胞救援療法を併用した大量化学療法第II床試験	JRSG	
Ewing肉腫	・限局性ユーイング肉腫ファミリー腫瘍に対する集学的治療法の第II相臨床試験	JESS	
神経芽腫	・進行神経芽腫に対する遅延局所療法早期第II相臨床試験	JNBSG	UMIN000000973
	・高リスク神経芽腫に対する標準的治療の後期第II相臨床試験	JNBSG	UMIN000001044
肝癌	・小児肝癌に対するJPLT-2治療プロトコール臨床第II相試験	JPLT	UMIN000001116
Wilms腫	・本邦における腎腫瘍に対する病期別統一プロトコール治療の完遂率と有効性の評価（JWiTS-2）	JWiTS	
髄芽腫またはテント上PNET	・小児髄芽腫/PNETに対する多剤併用化学療法と減量放射線療法の第II相試験	JPBTC	UMIN000000545
	・乳幼児髄芽腫/PNETに対する多剤併用化学療法および大量化学療法の第II相試験	JPBTC	UMIN000000546

*：試験IDは以下のサイトで検索した。
UMIN臨床試験登録システム（UMIN CTR）：http://www.umin.ac.jp/ctr/index-j.htm
財団法人日本医薬情報センター（JAPIC）臨床試験データベース：http://www.clinicaltrials.jp/user/cte_main.jsp
国立保健医療科学院 臨床研究〔試験〕情報検索：http://rctportal.niph.go.jp/
国立がんセンターがん情報サービス：http://ganjoho.ncc.go.jp/professional/med_info/clinical_trial/ct0120.html

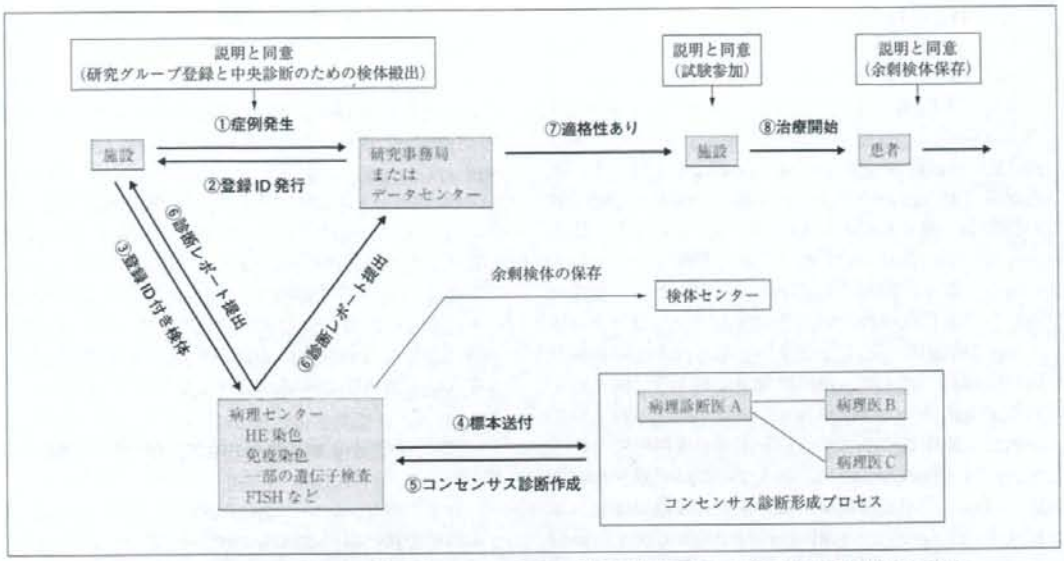

図1　小児がんの臨床試験登録と病理中央診断システム　我が国の小児がん臨床試験で一般的に行われている情報と検体の流れ，その中での病理中央診断システムと余剰検体保存の関連を示す．症例が発症した場合，施設は研究事務局あるいはデータセンターに登録申請を行い登録IDの発行を受ける(①②)．施設は患者検体に登録IDを付けて病理センターに送付する(③)．病理センターは必要な染色等を行った後，指定した病理医に標本を送付する(④)．病理医間でコンセンサス診断を作成し，病理センターを経由して診断レポートを施設ならびにデータセンターに送付する(⑤⑥)．試験参加の適格性の判断が施設に伝えられ治療が開始する(⑦⑧)．なお，このプロセスの中で，患者あるいは代諾者に対して，研究グループ登録と中央診断への検体搬出，試験参加，余剰検体保存，それぞれについて説明が行われ同意が取得される．

小児がんは稀少であるため，スタディクエスチョンを解決するためには，ある程度の症例数が必要となる場合がある．また，新しい臨床試験計画を独自で作成するための国内のエビデンスに乏しい場合もある．そのような場合には，海外で実施されている臨床試験に参加することも視野に入れた研究が展開されている．JPLSGが実施する試験のうち2件(ALCL99およびHLH-2004)は海外との共同研究である．

近年，臨床試験を実施するにあたっては試験内容を登録し公開することを義務づけようとする動きが高まってきている．その理由は，一般にネガティブデータは論文等で公表されない傾向があり，より透明性を確保することを目的としたものである．数年前に欧米の主要雑誌が協調し，事前に試験を登録して公開していない場合は論文掲載を行わない旨の発表を行った．以後，我が国でも登録制度と情報検索のシステムが整備されつつある．上記の研究グループが実施する臨床試験の多くが登録されており概要を検索することができる(**表2**脚注)．

Ⅱ．臨床研究グループと病理中央診断

さて，上記の各臨床研究グループが実施する臨床試験の多くで病理中央診断が実施されている．研究グループごとに複数の専任病理医を定めているが，その多くを日本病理学会小児腫瘍組織分類委員会のメンバーが担当している．病理中央診断の手順は試験ごとに作成される実施計画書に具体的に記載されているが，基本的には以下のごとくである(**図1**)．まず，試験に該当すると思われる患者が発生した場合，主治医は患者あるいは代諾者に，推測される疾患に該当する臨床試験への参加ならびに中央診断のための検体送付について説明し同意を得る．採取される検体やその処理方法は試験ごとに定められているが，病理中央診断の場合は，HE染色標本は必須で，それ以外に融合遺伝子検索などのため未固定検体の提出を求めているものもある．症例によっては免疫染色用に5～10枚程度の未染薄切標本提出を求めることもある．中央診断の

方法は一般には複数の病理医のコンセンサス診断としてレポートを作成し，標本を提出した施設ならびにデータセンター（または研究事務局）に連絡する．コンセンサス形成プロセスは研究グループごとに若干異なっている．一般には，例えば3名の診断医がいる場合，2名の診断が一致すればその診断を採用する，意見が異なれば，もう一人別の診断医の意見を求め2名の診断が一致すればそれを採用する，といった手法を採っている．意見が分かれる理由は多様である．多くの場合，標本が微量のため全体像がみえない，組織の挫滅，標本作成過程の何らかの理由による質の悪い標本などが原因になることが多いと思われる．純粋に学問的な理由，例えば，疾患概念がまだ十分に固まっておらず主観が入る余地がある．概念が確立されているが新たな指標によりさらに細分化される可能性のある場合も考えられるが，そのような場合は案外少ないと思われる．このような理由による意見の相違はむしろ歓迎すべきもので，多数例の検討でのエビデンス蓄積が重要であるし，研究グループとの連携による中央診断システムはそれらの解明を可能にしうるものである．

Ⅲ．小児腫瘍組織分類委員会の役割

日本病理学会小児腫瘍組織分類委員会は，日本小児外科学会，日本小児科学会からの協同の要請により設置され，1975年の小児腫瘍組織分類図譜第1篇小児肝癌，腎芽腫，神経芽腫群腫瘍の発刊をはじめとして，「癌取扱い規約」に相当する小児がんに関する分類図譜を編集・発行し，我が国における小児がんならびに関連疾患に関わる情報提供を通じて，疾患概念の認識と診断の標準化を目指すことを主たる業務としている．分類図譜はWHO分類や国際的に認知されている学術団体などが公表する最新分類に準拠し，我が国で普及させるための適切な形式に編集して定期的に発行している．以前は，「小児腫瘍組織分類図譜」という名称を使用していたが，2001年発行の版からは「小児腫瘍組織カラーアトラス」と名称変更しかつモダンなデザインの外観としている．

前述のごとく，当委員会のメンバーの多くが小児がんの臨床研究グループの中央診断担当医として参画してきたが，小児腫瘍組織分類委員会としてのまとまった活動ではなく，むしろボランティア的な活動であった．また，臨床研究グループに登録される症例は限られたものであるため，我が国の全体像を把握することはできないといった問題も明らかとなった（ただし，小児悪性リンパ腫の90％程度はJPLSGに登録されていると予想される）．これらの問題を解決する手段として小児腫瘍組織分類委員会が研究グループの中央診断に積極的に関与すると共に，研究に登録されない症例についても，いわばコンサルテーションのような形で中央診断できるシステム構築を現在考慮中である．このシステムを立ち上げるために，小児腫瘍中央診断委員会を小児腫瘍組織分類委員会内部に設置し，症例受付から始まる新診断システム考案，各臨床研究グループとの調整などの活動を開始した．なお，臨床試験に参加しない症例の追跡調査は重要な課題であり，それが実施可能な体制の整備をも目指している．

Ⅳ．診断後の余剰検体や研究用検体の有効活用

言うまでもないが，正確な診断がなされ，詳細な臨床情報が付いた患者検体は研究用リソースとして極めて価値が高い．患者検体を収集する方法を考えた場合，上記のような中央診断システムを利用することが効率的かつ現実的な方法である．実際には中央診断後の残余検体（余剰検体）について患者あるいは代諾者の同意の下に研究用リソースとして保存している場合が多い（**図1**）．さらには，これら検体は可能な限り一箇所に集約する動きにあり，国立成育医療センター研究所や千葉県がんセンター研究所などが検体センターとして機能している．このような中央診断後の余剰検体のみならず，初めから研究用に採取され使用される検体もある．これらの検体の残余分も貴重なリソースである．現在，臨床試験に関わる余剰検体が順調に集積されてきているが，問題点としては，このような貴重なリソースをどのような取り決めで使用していくかについてのコンセンサスが未だ形成されていない点である．米国最大の小児がん研究グループであるChildren's Oncology Group（COG）では，中央診断システムならびに検体センターをコロンバスにあるNationwide Children's Hospital一箇所に集約し，また，配分ルールもグループ内でのコンセンサスとして決定している．それらも参考にしながら我が国でも共有リソースの使用ルールを決める必要がある．

Ⅴ．米国における小児がん臨床試験と中央診断，検体保存

米国では，数年前に幾つか個別に活動していた小児がん研究グループがCOGという一つの大きな枠組み

の中で活動するようになった．各種レベルの臨床試験の推進のみならず，中央診断システム構築，余剰検体の保存と活用，長期フォローアッププログラムの開発など多角的な活動を展開している．前述のようにCOGにおける中央診断と検体保存のセンターはNationwide Children's Hospital（Columbus Children's Hospitalから最近名称変更，http://www.nationwidechildrens.org）内のBiopathology Center（http://www.biopathologycenter.org）に全て集約されている．そもそもは，同病院病理のStephen J. Qualman博士が始めた事業であるが，現在は極めて高度に発展したシステムとなっている（Qualman博士は昨年引退され，Nilsa C. Ramirez博士が後継者として就任している）．米国には1980年代より全米のがんを対象としたCooperative Human Tissue Network（CHTN，http://www.chtn.nci.nih.gov）がNCIの資金により構築されており，1991年にはすでにPediatric Divisionが出来上がってColumbus Children's Hospitalがセンターとして指名されている．CHTNは検体を収集して中央に保存するというシステムではなく，検体は各施設で保存し情報だけを中央に集めて共有し，必要に応じて配分するというバーチャルバンキングシステムである．現在は，小児がんの多くがCOGの中で診断され治療されるため検体もCOG経由でBiopathology Centerに集められるが，スタディに参加しない症例の検体も有効活用できるシステムとなっている．

COGが行う臨床試験に関わる病理中央診断についても，いったん全ての検体がCOGに集められ，必要な染色等を行ったうえで病型別に定められた病理医に送付されるという形態をとっている．なお，Biopathology CenterにはVIPER（Virtual Imaging for Pathology Education & Research，http://viper.epn.osc.edu/viper/）と呼ぶバーチャルスライドユニットが存在する．オハイオ大学のスーパーコンピュータと共同で開発しており，診断そのもの，診断の標準化および教育といった目的のために活用されている．Biopathology Centerは小児がんのような稀少疾患の研究を推進するための一つの究極の形かもしれない．

Ⅵ．小児がん登録

疾病の基本情報の収集や分析といった地道な活動は我が国では大変立ち遅れている．がん登録もその一つで，昨年成立したがん対策基本法にも盛り込まれず，付帯事項として記載され，がん対策推進計画の中で計画の一つとして表現されるにとどまった．小児がん登録も言わずもがなの状況であり，推進計画の中には言葉としては出てくるが，小児がんを計画に盛り込んでいる自治体は皆無である．地域がん登録は2008年5月現在35道府県市で実施されているがその中で小児がん登録を意識的に位置づけているところは大阪府のみである．ただし，大阪府の場合も意識の高い小児科医の献身的な努力によって支えられているのが現状である．このような状況の中，小児がんの診療に関わる医師たちが学会ベースで小児がんの全数把握に取り組む計画を立案中である．日本小児外科学会（http://www.jsps.gr.jp/public/registration.htm），日本小児血液学会（http://www.jsph.info/osirase/JSPH-touroku.html）ならびに日本小児がん学会（http://www.ccaj-found.or.jp/jspo/general/index.htm）はそれぞれ独自に小児がん登録を実施してきたが，登録率の向上，国際比較の必要性などを考慮し，日本小児がん学会が関連学会と連携して従来より精度の高い小児がん登録を実施する計画を立てている．小児がんの国際比較には，International Classification of Diseases for Oncology 3rd Edition（ICD-O）に基づいたInternational Childhood Cancer Classification 3rd Edition（ICCC-3）[4]が使用されているため，日本小児がん学会が収集する情報を最終的にICCC-3に従って編集できるように現在使用中の登録票ならびに登録方法を改訂中である．

小児がん患者の生存率が70%ないし80%となり長期にわたる生存が期待できる状況となって，小児がん登録に求める役割に変化が起こりつつある．すなわち，二次がん発生やその他の各種晩期合併症の発生をも把握できるシステムづくりを目指すべきとの意見が広まりつつある．国と自治体が連携して推進する地域がん拠点病院構想や学会主導のがん治療認定医制度や認定施設制度の定着と広がりの中で，小児がんについても成人と同じように診療体制の整備が必要であり，小児がん登録もその中に組み込まれるべきものであると考える．

おわりに

我が国における小児がんに関する質の高い臨床研究は始まったばかりと言える．病理医はこのような研究の枠組みの中でかなり重要な役割を演じる必要がある．数年間の経験からは，ある種の小児がん病型では

中央診断と施設診断の間で不一致率が10%を超えるものもあった．これらの情報をいかに現場に還元していくかは中央診断を担当する病理医ならびに小児腫瘍組織分類委員会に課せられた課題であると考える．精度の高い診断を達成するためには，医療現場の病理医の協力が必須であり，今後，学会や書物を通じて小児がんの臨床研究における病理医の活動を広く宣伝，紹介してゆきながら理解を得てゆきたいと考えている．コロンバスのBiopathology Centerの現責任者Ramirez博士との会話では，検体配分についても彼女が大変強い権限をもっていることがわかった．診断のみならず検体保存や配分に際しても病理医は強い指導力を発揮すべきなのだと思う．今後，我が国ではがん診療拠点病院のネットワークが構築されてゆくが，それらの病院では院内がん登録が義務づけられる．そのような場面でも病理医は指導的な役割を発揮するのだと思う．その際，小児がんにもご留意いただけると大変ありがたいと思う次第である．

文　献

1) 森川康英：小児横紋筋肉腫に対する中央病理診断及び遺伝子診断に基づく臨床試験の確立と新規治療法開発に関する研究，がん研究助成金報告書（http://ganjoho.ncc.go.jp/pro/mhlw-cancer-grant/2005/keikaku/17-13.pdf）
2) 国立がんセンターがん対策情報センター：がん情報サービス，小児がんシリーズの冊子「小児のユーイング肉腫について」（http://ganjoho.ncc.go.jp/public/qa_links/brochure/child.html）
3) 越永従道，七野浩之，福澤正洋：小児腎腫瘍における治療成績と方針．小児科診療 2005，68：1643-1650
4) International Classification of Childhood Cancer, 3rd ed., SEER International Classification of Childhood Cancer（http://seer.cancer.gov/iccc/）を参照．また，United Kingdom Association of Cancer Registriesよりダウンロード可能（http://82.110.76.19/coding/iccc3.pdf）

original article

Annals of Oncology 20: 166–174, 2009
doi:10.1093/annonc/mdn562
Published online 20 August 2008

Childhood cancer in Japan: focusing on trend in mortality from 1970 to 2006

L. Yang[1], J. Fujimoto[2], D. Qiu[1] & N. Sakamoto[1]*

[1]*Department of Maternal and Child Health, National Research Institute for Health and Development;* [2]*National Research Institute for Health and Development, Tokyo, Japan*

Received 11 July 2008; accepted 14 July 2008

Objective: This paper describes the mortality rates and trends from childhood cancer at the population level over a 37-year period in Japan and other developed countries.

Materials and methods: Age-standardized mortality rates were calculated by the direct method using age-specific mortality rates at 5-year age intervals and weights based on the age distribution of the standard world population. The joinpoint regression model was used to describe changes in trends.

Results: For all cancers combined, the mortality rate during 2000–2006 was 2.20 per 100 000 population for boys and 1.89 for girls. Mortality for all cancers combined decreased since 1970s in Japan. A stable trend was observed in recent 5 years for girls. For leukemia, a declining trend was observed in the whole period for girls and in 1976–2006 for boys. Mortality rates for childhood central nervous system tumors have remained stable at a low level during 1980–2006.

Conclusions: The present study provides updated figures and trends in childhood cancer mortality in Japan and other developed countries. This will help to estimate care needs and to plan intervention and the quantity of appropriate childhood cancer treatment.

Key words: cancer, childhood, epidemiology, mortality, time trends

original article

introduction

It is estimated that ~3000 Japanese children aged from birth to 18 years will develop cancer. Although childhood cancer is rare compared with adult cancer, it is the fourth most common cause of death among children aged 0–14 years in Japan, according to the report given by the Ministry of Health, Labor and Welfare of Japan in 2005. A population-based study in Osaka prefecture in Japan indicated that death due to childhood cancer declined from 1972 to 1995, while the incidence increased in the same period [1]. In the United States, an estimated 10 400 new cases and 1545 deaths are expected to occur among children aged 0–14 years in 2007 [2]. During recent three decades, the incidence of childhood cancer increased ~0.6% annually. In contrast, mortality from childhood cancer declined by 1.3% per year during 1990–2004 [3]. A population-based study among European children since the 1970s showed that the overall incidence of childhood cancer has increased by 1.0% per year, while mortality has declined by 3.6% per year in the past three decades [4, 5].

The decrease in mortality from childhood cancer has been suggested to be due to the effects of improvements in diagnosis and therapy. For all childhood cancers combined, 5-year relative survival has improved markedly over the past three decades, from <50% before the 1970s to ~80% today [2].

There is no national childhood cancer registry system in Japan, and recent childhood cancer mortality has not been well characterized in terms of temporal and geographic trends. This paper describes the occurrence of death from childhood cancer at the population level over a 37-year period in Japan using official death certification data, which record 100% of deaths in Japan. The aim of this study was to ascertain the general mortality trend for each sex and to study the moment at which a shift in the trend occurred.

materials and methods

The number of death by cause, stratified for sex and by 5-year age group for cancer for the period 1970–2006, was derived from vital statistics compiled by the Ministry of Health, Labor and Welfare of Japan. Population figures were obtained from census data and intercensus estimates, by calendar year, age and gender. Population censuses of Japan are conducted every 5 years by the Statistics Bureau, Ministry of Internal Affair and Communications. For comparison, we also calculated the cancer mortality rate in other developed countries, including Canada (1970–2004), the United States (1970–2005), Italy (1970–2003), UK (1970–2005) and New Zealand (1970–2004). Deaths at age 0–4, 5–9 and 10–14 years were derived from the World Health Organization (WHO)

*Correspondence to: Dr N. Sakamoto, The Division of Epidemiology, Department of Maternal and Child Health, National Research Institute for Child Health and Development, 2-10-1 Ookura, Setagaya-ku, Tokyo 157-8535, Japan.
Tel: +81-03-3416-0181(4360); Fax: +81-03-5494-7490; E-mail: sakamoto@nch.go.jp

mortality database. Estimates of the population, generally based on official censuses, were based on the same WHO database.

During the study period, three different revisions of the International Classification of Disease were used. In Japan, this included International Classification of Diseases (ICD)-8 from 1970 to 1978, ICD-9 from 1979 to 1994 and ICD-10 from 1995 onward. Since the differences were minor in various revisions, we recorded six cancer sites, including all cancer combined (ICD-8: 140–209; ICD-9: 140–208; ICD-10: C00–97), leukemia (ICD-8: 204–207; ICD-9: 204–208; ICD10: C91–C95), lymphomas (ICD-8: 200–202; ICD-9: 200–202; ICD-10: C81–85), central nervous system (CNS) tumors (ICD-9: 191–192; ICD–10: C70–C72), malignant kidney tumors (ICD-8: 189; ICD-9: 189; ICD-10: C64–C68) and malignant bone tumors (ICD-9: 170; ICD-10: C40–C41). In order to avoid possible bias due to changed ICD, the analysis of CNS tumors, malignant bone tumors and lymphomas (United States only) was restricted to data from 1980 onwards.

Age-standardized mortality rates were calculated by the direct method using age-specific mortality rates for 5-year age intervals and weights based on the age distribution of the standard world population. All rates are expressed per 100 000 children-years.

Table 1. Childhood cancer mortality rate (per 100 000) in Japan and other selected countries (boys)

Period of death	Japan	Canada	United States	Italy	UK	New Zealand
Total malignant tumors						
1970–1974	6.19	7.69	6.47	8.72	7.20	8.45
1975–1979	5.86	6.10	5.25	7.96	6.53	7.59
1980–1984	4.99	5.34	4.60	6.96	5.06	7.04
1985–1989	4.13	4.52	3.74	5.50	4.13	7.17
1990–1994	3.37	3.43	3.33	5.40	3.96	4.94
1995–1999	2.90	2.82	2.87	4.53	3.42	4.83
2000–	2.20	2.65	2.68	3.64	3.00	3.58
Leukemia						
1970–1974	3.39	3.58	2.90	3.94	3.02	3.44
1975–1979	3.10	2.81	2.23	3.50	2.79	3.07
1980–1984	2.46	2.06	1.76	2.85	2.11	2.89
1985–1989	1.91	1.79	1.41	2.20	1.52	2.76
1990–1994	1.54	1.17	1.20	1.99	1.41	1.69
1995–1999	1.21	0.90	0.97	1.64	1.18	1.99
2000–	0.84	0.85	0.85	1.25	0.91	0.78
Lymphomas						
1970–1974	0.61	0.76	–	1.14	0.73	0.77
1975–1979	0.66	0.62	–	0.86	0.65	0.75
1980–1984	0.65	0.49	0.39	0.62	0.40	0.51
1985–1989	0.55	0.32	0.31	0.51	0.29	0.58
1990–1994	0.36	0.21	0.23	0.47	0.25	0.15
1995–1999	0.18	0.16	0.16	0.41	0.20	0.23
2000–	0.14	0.12	0.12	0.27	0.20	0.12
Central nervous system tumors						
1980–1984	0.40	1.17	0.95	1.41	1.12	1.50
1985–1989	0.40	1.18	0.86	1.05	1.10	1.66
1990–1994	0.46	0.97	0.86	1.19	1.10	1.79
1995–1999	0.49	0.83	0.79	0.93	0.94	1.35
2000–	0.43	0.81	0.75	0.87	0.85	1.43
Malignant kidney tumors						
1970–1974	0.18	0.35	0.24	0.45	0.33	0.34
1975–1979	0.16	0.20	0.17	0.34	0.26	0.33
1980–1984	0.12	0.13	0.14	0.23	0.20	0.24
1985–1989	0.09	0.10	0.10	0.19	0.09	0.22
1990–1994	0.07	0.06	0.09	0.13	0.12	0.26
1995–1999	0.06	0.05	0.08	0.13	0.13	0.09
2000–	0.05	0.12	0.08	0.09	0.09	0.08
Malignant bone tumors						
1980–1984	0.15	0.18	0.16	0.33	0.26	0.12
1985–1989	0.15	0.16	0.12	0.24	0.18	0.30
1990–1994	0.14	0.11	0.11	0.19	0.14	0.04
1995–1999	0.13	0.12	0.11	0.14	0.13	0.17
2000–	0.09	0.12	0.13	0.15	0.15	0.24

The joinpoint regression model was used to describe changes in trends [6]. We allowed for up to four joinpoints for each model. The computation of mortality rates and their standard errors was implemented in SAS 9.0. Joinpoint analyses were carried out using Joinpoint software 3.3.1 from the Surveillance Research Program of the US National Cancer Institute. Time trends were assessed for all childhood cancer combined and for six major categories, including leukemia, lymphoma, malignant brain tumor, malignant kidney tumor and malignant bone tumor.

The standardized mortality ratio (SMR) by sex was calculated for 47 prefectures in Japan by taking the ratio of the observed to expected deaths. The z-value was computed for each SMR, on the basis of the assumption that observed deaths follow a Poisson distribution. The maps were developed using adjusted SMR by gender.

results

mortality

Tables 1 and 2 give age-adjusted mortality rates in Japan and five other developed countries for all malignant tumors and for

Table 2. Childhood cancer mortality rate (per 100 000) in Japan and other selected countries (girls)

Period of death	Japan	Canada	United States	Italy	UK	New Zealand
Total malignant tumors						
1970–1974	5.10	6.12	5.13	6.90	5.55	6.85
1975–1979	4.61	4.83	4.07	5.90	4.69	6.35
1980–1984	3.88	4.24	3.59	5.48	4.27	4.39
1985–1989	3.30	3.43	3.06	4.36	3.81	5.27
1990–1994	2.75	2.80	2.69	4.19	3.01	3.81
1995–1999	2.23	2.73	2.39	3.29	2.65	3.54
2000–	1.89	2.06	2.28	2.86	2.47	3.06
Leukemia						
1970–1974	2.86	2.80	2.26	3.28	2.43	3.08
1975–1979	2.50	2.34	1.70	2.53	1.82	1.86
1980–1984	1.79	1.71	1.30	2.17	1.59	1.66
1985–1989	1.50	1.37	1.09	1.51	1.26	1.84
1990–1994	1.20	0.89	0.91	1.47	0.89	1.04
1995–1999	0.88	0.87	0.78	1.07	0.91	1.34
2000–	0.68	0.46	0.69	0.82	0.76	0.90
Lymphomas						
1970–1974	0.33	0.39	–	0.54	0.31	0.27
1975–1979	0.35	0.18	–	0.39	0.27	0.41
1980–1984	0.31	0.23	0.16	0.26	0.22	0.21
1985–1989	0.28	0.22	0.13	0.28	0.14	0.25
1990–1994	0.25	0.12	0.09	0.16	0.09	0.10
1995–1999	0.10	0.09	0.08	0.17	0.09	0.20
2000–	0.06	0.39	0.06	0.18	0.09	0.05
Central nervous system tumors						
1980–1984	0.39	1.01	0.84	1.13	0.93	1.43
1985–1989	0.38	0.88	0.77	0.99	0.98	1.37
1990–1994	0.44	0.75	0.77	0.90	0.88	1.26
1995–1999	0.47	0.84	0.71	0.72	0.74	0.88
2000–	0.42	0.69	0.69	0.78	0.71	1.00
Malignant kidney tumors						
1970–1974	0.20	0.32	0.25	0.44	0.37	0.38
1975–1979	0.11	0.23	0.19	0.33	0.26	0.36
1980–1984	0.12	0.13	0.15	0.27	0.18	0.00
1985–1989	0.07	0.11	0.13	0.18	0.18	0.10
1990–1994	0.07	0.10	0.09	0.18	0.15	0.27
1995–1999	0.05	0.14	0.11	0.11	0.12	0.21
2000–	0.06	0.11	0.10	0.10	0.12	0.11
Malignant bone tumors						
1980–1984	0.17	0.20	0.16	0.26	0.29	0.13
1985–1989	0.16	0.14	0.12	0.27	0.26	0.31
1990–1994	0.12	0.13	0.13	0.23	0.14	0.05
1995–1999	0.14	0.12	0.11	0.16	0.13	0.18
2000–	0.11	0.16	0.11	0.12	0.20	0.25