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Review

The International Neuroblastoma Risk Groups (INRG): a Preliminary Report

R.P. Castleberry, J. Pritchard, P. Ambros, F. Berthold, G.M. Brodeur, V. Castel, S.L. Cohn, B. De Bernardi, C. Dicks-Mireaux, D. Frappaz, G.M. Haase, M. Haber, D.R. Jones, V.V. Joshi, M. Kaneko, J.T. Kemshead, P. Kogner, R.E.J. Lee, K.K. Matthay, J.M. Michon, R. Monclair, B.R. Roald, R.C. Seeger, P.J. Shaw, H. Shimada and J.J. Shuster

The International Neuroblastoma Working Group sponsored by the William G. Forbeck Research Foundation, Hilton Head Island, South Carolina, U.S.A. and the Neuroblastoma Society of the United Kingdom

INTRODUCTION

NEUROBLASTOMA IS the most common solid malignancy of childhood. The enigmatic nature of this tumour has long been recognised [1]; some tumours demonstrate spontaneous resolution following minimal or no therapy while others present at diagnosis with widely spread disease and are virtually always associated with poor survival in spite of modern therapy. In large part, improvements in outcome of children with neuroblastoma have stemmed from a greater ability to distinguish cases of varying risk allowing therapy to be tailored according to risk of recurrent disease. Previously, prognostic stratification was based on stage and age alone but more recently has also incorporated selected biological features. The refinement of clinical/biological prognostication models has been impeded by (1) the different systems for staging and evaluating neuroblastoma used by the principal neuroblastoma research groups worldwide and (2) by the lack of patient numbers required to conduct the multivariate analyses necessary for distinguishing the most predictive groupings of clinical and biological features.

Beginning in 1986, there have been a series of conferences, sponsored by the William Guy Forbeck Research Foundation and the Neuroblastoma Society of the United Kingdom, to address these problems and initiate strategies to overcome them. The first meeting in Hilton Head, South Carolina, U.S.A., convened clinical and laboratory neuroblastoma researchers from 13 countries and focused upon standardising staging and clinical assessment. The result was the development of the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Response Criteria (INRC) [2]. The INSS/INRC combined the most frequently used systems and definitions in the countries represented [3–6] and, for the first time, provided an opportunity for the international neuroblastoma research community to generate data from clinical and laboratory studies which could be compared. When the INSS/INRC were applied over the ensuing 4 years, some problems with interpretation were identified which impeded universal implementation [7]. This prompted the second INSS/INRC workshop in October, 1991. While major revisions in the INSS/INRC were not necessary, the areas of contention were clarified and it was agreed that the changes made would streamline integration of the INSS/INRC into the neuroblastoma research community [8]. The revised INSS criteria, detailed in Table 1, have gained universal acceptance.

The second INSS/INRC working group also discussed the emerging importance of biological variables for predicting outcome, independent of stage and age. It was recommended that a prospective effort be launched to construct and evaluate International Neuroblastoma Risk Groups (INRG), representing a composite of age, INSS stage and the most predictive biological variables [8]. Such was the proposed objective for the third INSS/INRG conference. Before embarking on this study, three specific aims had to be realised: (1) to determine which biological variables, based upon universal availability and prognostic power, should be incorporated into the INRG; (2) to develop the infrastructure necessary to test the INRG and (3) to assess the feasibility of combining data sets from the various neuroblastoma research groups worldwide. To accomplish these aims, three international subcommittees (Pathology, Immunobiology, Statistics) were established (Figure 1). We report here a summary of the deliberations of these subcommittees and of the third meeting of the INSS/INRG working group (Berkeley, U.K., September, 1995).

INSS CRITERIA

While the principal focus of INSS/INRG 3 was to develop the INRG, the participants did discuss the revised INSS criteria. It was agreed that with the increasing familiarity with the INSS criteria, major changes were neither desirable

Correspondence to R.P. Castleberry. The Children's Hospital of Alabama, 1600 7th Avenue South, Birmingham, Alabama, U.S.A.

nor warranted. However, it was acknowledged that one amendment was indicated based upon evidence recently reported by the Pediatric Oncology Group and the Children's Cancer Group [9, 10]. Specifically, both groups noted that the presence of involved, non-adherent lymph nodes in infants (<1 year of age) does not adversely affect prognosis. Therefore, the systematic search for and sampling of lymph nodes in these patients seems hardly justified and should be abandoned.

The participants also emphasised the importance of obtaining sufficient tissue for biological studies from patients with more advanced disease (INSS stages 3 and 4).

The need to understand the biology of this subset of neuroblastic tumours better so rational treatment strategies can be designed seems to outweigh the risks involved in obtaining this tissue. This is especially true considering that most of these children will have general anaesthesia for the placement of venous access catheters.

Table 1. *INSS criteria* [8]

Stage	Definition
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral nonadherent† lymph nodes negative for tumour microscopically
2A	Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral, non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline,‡ with or without regional lymph node involvement or localised unilateral tumour with contralateral regional lymph node involvement or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stages 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow* (limited to infants < 1 year of age)

*Marrow involvement in stage 4S should be minimal, i.e. <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan, if performed, should be negative in the marrow. †Lymph nodes attached to and removed with the primary tumour. ‡The midline is defined as the vertebral column. Tumours originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

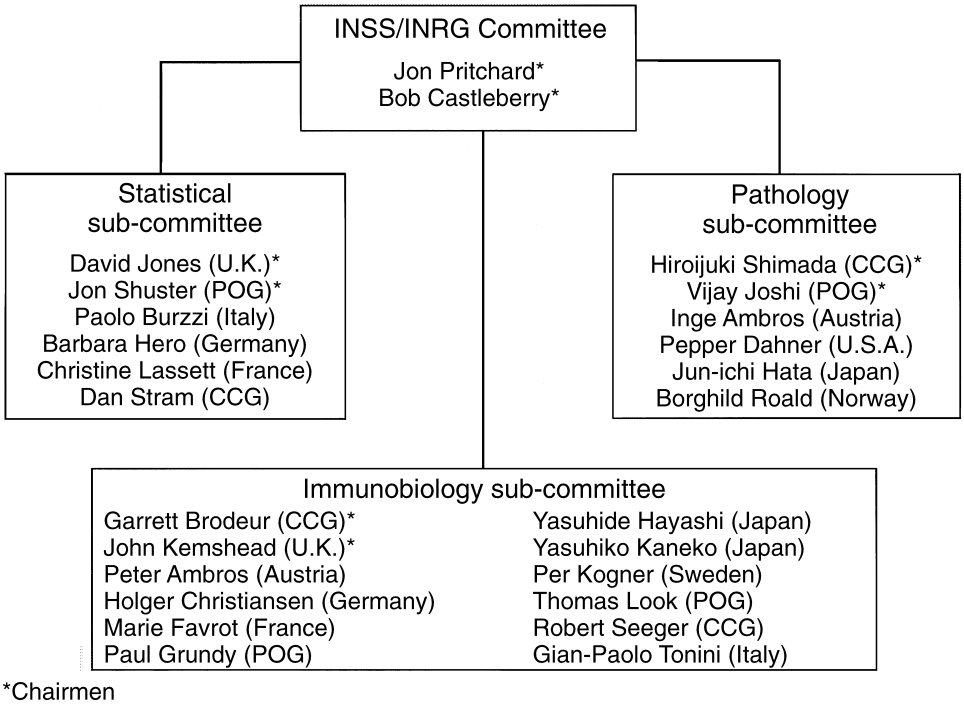

Figure 1. Subcommittees of the INSS/INRG Working Group.

Table 2. Availability of biological prognostic variables

Research group	LDH/ferritin	*MYCN*	1p deletions	Histopathology	Ploidy	*trk*-A	CD44	MRP
Italy	√	√	√	√	√	N	N	F
ANZ/SCSG	√	√	F	N	√	√	N	√
Austria	√	√	√	√	√	F	√	F
USA/CCG	√	√	√	√	F	√	F	F
Germany	√	F	F	√	√	N	√	F
Japan	√	√	N	√	√	N	N	N
Norway	√	√	√	N	√	√	F	N
USA/POG	√	√	√	√	√	F	N	F
Spain	√	√	F	√	√	F	F	N
France	√	√	√	F	√	F	F	N
United Kingdom	√	√	F	√	F	N	F	N

√=available; F, available in the near future; N, not available and not being developed; MRP, multidrug resistance associated protein; CCG, Children's Cancer Group; POG, Pediatric Oncology Group.

IMMUNOBIOLOGY

The Immunobiology subcommittee canvassed the major neuroblastoma study groups regarding the availability of the biological features which furnish proven or potential prognostic information. Detailed in Table 2 are the eight most frequently assessed prognostic features being evaluated in 11 neuroblastoma research groups. Serum lactate dehydrogenase (LDH)/ferritin, *MYCN* copy number, 1p deletions and ploidy were being consistently assessed or were evolving in 91% of the research groups; histopatholgy in 82%. These variables were considered ideal candidates for the INRG model by virtue of their international availability and prognostic potential. In contrast, *trk*-A, CD44, and multidrug resistance associated protein (MRP), while having potential prognostic value, were available in less than 65% of the groups.

This subcommittee also provided specific guidelines for the procurement and processing of tissue, including the volume needed to study the proposed features; these details will be reported more completely elsewhere. The advantages and disadvantages of both open and non-invasive (needle) biopsies were discussed at length. The principal objection to non-invasive techniques was the lack of adequate tissue for histopathology.

PATHOLOGY

Although many histopathological criteria for categorizing neuroblastic tumours and predicting patient outcome have been reported [11–16], the absence of their universal application and their reproducibility among pathologists has impeded the assessment of these features as independent predictors of prognosis. Notwithstanding these problems, the prognostic potential of histopathological features noted by Shimada and associates [15] and Joshi and associates [16] strongly suggests that histopathology be incorporated into the multivariate analyses for the INRG. Therefore, it was vital that consistency be introduced into this area. The International Pathology Subcommittee, through discussions and practical sessions, developed common terminology and criteria for the diagnosis of ganglioneuroma, ganglioneuroblastoma and neuroblastoma and its subtypes (undifferentiated, differentiating and poorly differentiated). Further, a preliminary agreement was accepted regarding histopathological features which had prognostic value, reflecting tumour type and subtype, the degree of differentiation, the rate of mitosis, the process of cell death, and the amount of overall tumour necrosis. Concordance studies of 230 blinded specimens were conducted for both diagnostic and prognostic features. Agreement was highest for differentiation (89%), polymorphism (89%), mitotic rate (85%) and calcification (96%). For the mitotic karyorrhexis index (MKI), concordance was less (75%). In spite of some disagreements, pathology participants were enthusiastic that histopathology could be incorporated into the INRG model with a high level of concordance and accuracy.

The final international histopathology criteria will be reported in detail elsewhere. To assist in the incorporation of these definitions and criteria into the international pathology community, an atlas will be prepared and made available to neuroblastoma groups worldwide.

STATISTICS

The International Statistical Subcommittee explored the feasibility of interfacing databases from various research groups by successfully centralising at the University of Florida the datasets from more than 2800 neuroblastoma cases. To investigate methods for creating and testing the INRG, and using this international database, a preliminary INRG model was developed based on age (<1 year versus ≥1 year), Evans stage (since this was recorded most consistently among the databases sampled), serum LDH/ferritin and *MYCN* copy number. Using partitioning analysis [14] where prognostically distinct patient subsets are separated and similar prognostic subsets are amalgamated, four clinical groupings were identified (Table 3). By analysing the biological variables within these clinical groups, clinical/biological subsets were formed. Specifically, cases were moved to a lower risk group if two of the three biological variables were favourable and the third was either favourable or missing from the dataset. Notwithstanding the obvious statistical hazards of this

Table 3. Pilot INRG analysis: clinical risk groups

Group A	All patients, Evans stage I
	<1 year, Evans stage II
Group B	≥1 year, Evans stage II
	<1 year, Evans stage III, IV
Group C	≥1 year, Evans stage III
	<1 year, Evans stage IV
Group D	≥1 year, Evans stage IV

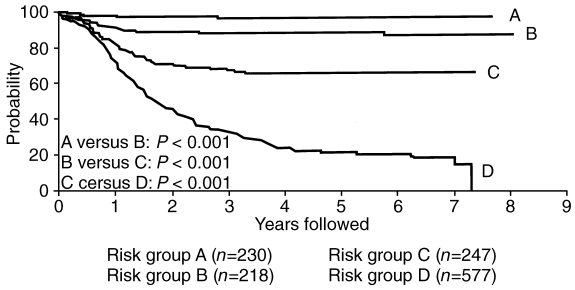

Figure 2. Survival by risk group INSS 3—feasibility analysis.

Table 4. *INRG study — hypothesis and objectives*

Hypothesis	When coupled with INSS stage and age, select biological variables will define three distinct risk categories requiring different therapy
Objectives	To determine by multivariate analyses which and what combination of biological variables are most powerful in changing predictive outcome of INSS stage and age-related categories To establish an international cooperative network for re-evaluating the INRG when new biological features with prognostic potential or newer therapy becomes available

being a retrospective analysis where not all data was available from all cases and in which the intensity of therapy was not accounted for, the identification of four distinct survival groups (Figure 2) confirmed that this methodology is feasible and would provide valid results using prospectively collected data.

THE INRG STUDY

Based on these preliminary observations and experiences, the conferees agreed that a prospective INRG study was both feasible and warranted. The study hypothesis and objectives are listed in Table 4. When treatment is accounted for, it is anticipated that three biological subtypes, previously hypothesised by Brodeur and associates [19], will be identified. All international neuroblastoma research groups will be invited to contribute cases in which prospectively collected data regarding age, INSS stage, *MYCN* copy number, 1p deletions, ploidy, histopathology and serum LDH/ferritin are available. For participating laboratories, quality control measures will be provided by the International Immunobiology Committee. The intensity of therapy will be accounted for using a model similar to that reported by Cheung and associates [20]. To allow for patient non-evaluability due to incomplete data, for high statistical power and for analyses within prognostic groups, the accrual target for the INRG study will be 2000. As in the pilot study, the INRG will be created by recursive partitioning using even case numbers to establish the INRG and odd case numbers to test the INRG.

The INRG infrastructure will also provide a perpetual international interaction, assuring that the INRG will continue to evolve as newer biological variables become universally available and better treatment for higher risk disease is established.

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