Request for INRG Data Analysis

Proposal Title: _**Analysis of late relapses in high risk neuroblastoma patients**

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Application page limit (5 pages)

Please format proposal as follows:

Hypothesis:
With the incorporation of multimodal therapy, a small proportion of patients with relapsed high risk neuroblastoma can experience long-term survival. This population can be identified with clinical and biological factors and will need specific therapeutic approaches.

Patient Cohort (Eligibility Criteria):

- Patients aged ≥18 months with stage M
- Date of diagnosis 1998 – 2011

Background:
Outcome for high risk neuroblastoma has improved with the incorporation of multimodal therapy including intensive chemotherapy, local control with surgery and radiotherapy, high dose chemotherapy, differentiation therapy and immunotherapy.

Still, approximately 40% of patients with high risk neuroblastoma will experience relapse (Park, ASCO 2016). Multiple reports including the INRG have reported very poor long term outcomes for children with relapsed neuroblastoma. In an analysis of the INRG cohort, 5-year overall survival (OS) was 8% for children with stage 4 neuroblastoma, and 4% for those with MYCN amplification. In this analysis, patients experiencing early relapses had worst outcomes compared to those relapsing >18 months after diagnosis (London, JCO 2011).

Although the occurrence of late relapses was reported in the ENSG database 15 years ago (Cotterill and Pearson, Med Ped Oncol 2001), little is known about this patient

population. In this analysis, out of 82 patients aged >1 year with stage 4 disease that had survived for 5 years, 13 experienced relapses beyond 5 years (15.9% of 5-year survivors).

This patient population has a longer event-free period from first to subsequent relapses when compared to patients who relapse early and hence, they receive a wide variety of therapeutic options. However, there is a lack of knowledge about the natural history of this patient population and no international agreement on what the best therapeutic strategy is.

It is therefore necessary to describe the patient population who relapse late; specifically the cut-off that defines a late relapse, the baseline characteristics of patients who relapse late, the outcome of these patients and the factors that influence outcome and whether a population of these patients who relapse late can be salvaged long-term.

Significance:

This analysis will help to identify the population of high risk patients experiencing late relapse, improving our knowledge about this population, their characteristics and outcome and understanding their clinical course. The data will help clinicians informing families and patients at the time of relapse of expected outcomes and expectations. Eventually, this will help designing treatment strategies for relapsed neuroblastoma encompassing different treatment modalities, e.g. chemotherapy, immunotherapy, MIBG therapy.

Proposal description:

Study objectives

1. To describe the OS of patients older than 18 months at diagnosis with Stage M high risk neuroblastoma in the INRG database, overall and partitioned on the basis of the timing of first relapse (testing 6-monthly cut-offs from 5-10 years post diagnosis
2. To identify a group of patients with late relapses as defined by an optimal cut-off of time to first relapse that maximizes the difference in the risk of death, within Stage M high risk neuroblastoma patients older than 18 months (compared with those having earlier relapses)
3. To describe the incidence, characteristics and post-relapse survival of the patient population experiencing late relapses
4. To determine whether there is a population of children with late relapses that are long-term survivors
5. To identify clinical and biological (including segmental chromosomal aberrations already reported in INRG database) characteristic features *at presentation* that are prognostic of post-relapse survival, within patients with Stage M neuroblastoma >18 months

Analytic methods:

For inferential testing, the data will be divided at random into a test and validation set. If the inferential results are similar in the test and validation sets, the sets will be combined for greater power in an overall definitive analysis.

1. We will generate Kaplan-Meier curves of OS, overall and by partitions of time to first relapse/PD/death at 6-monthly intervals from 5-10 years.
2. At each cut-off, we will compare the event free survival (EFS) of those with early versus late/no relapse/progressive disease (PD)/death using a Cox proportional

hazard regression model. The optimal cut-off will be defined as the one with the largest hazard ratio, out of the cut-offs that produce a p-value <0.05.

3. The proportion of patients by site(s) of disease will be compared for early versus late/no relapse/PD/death. 95% confidence intervals will be placed on the proportions.
4. A logistic regression model (dependent variable: 0=late/no relapse/PD/death; 1=early relapse/PD/death) will be used to identify factors that predict early vs late/no relapse/PD/death. For a given independent variable, the increased risk for relapse/PD/death will be quantified by the odds ratio. After testing each factor in a univariate model, multivariable testing will be performed using backwards stepwise selection starting from factors that were statistically significant in the univariate model.
5. To facilitate application of these findings, a nomogram will be constructed including each of the statistically significant factors (Iasonos, JCO 2008).

Data Requested:

We request use of all data items in the INRG database for the cohort of patients eligible for this study, and diagnosed between 1998 and 2011.

If you would like to perform the analysis locally, in lieu of using an INRG statistician, please include the CV of your biostatistician and provide a detailed statistical plan.

Please upload your proposal as a Word document or PDF as part of a project request on the INRG Cohort Discovery site (http://cohortdiscovery.inrgdb.org).

Questions can be sent to: support@inrgdb.org

Collaborators:

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