Request for INRG Data Analysis

Proposal Title: Factors predictive of survival after relapse in patients with high-risk neuroblastoma

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Application page limit (5 pages)

Please format proposal as follows:

Specific Aims:

1. Describe changes in survival time after disease recurrence in patients with high-risk neuroblastoma as a function of year of diagnosis (1990-present)
2. Explore the impact of clinical and biological factors present at diagnosis that predict survival time after disease recurrence in patients with high-risk metastatic neuroblastoma, in the context of modern therapy (2002-present)
3. To develop multivariable models to explore the impact of these individual factors in combination in predicting post-relapse survival, in the context of modern therapy (2002-present)

Hypothesis:

This proposal is intended to build on previous published INRG analyses [1,2] in two important ways. First, the INRG dataset has expanded considerably since these original publications with the incorporation of significant additional data from COG (and hopefully in the near future also from SIOPEN), as well as the addition of more biological data (such as that relating to segmental chromosomal abnormalities). Second, both of these previous analyses have focused on the entire population of neuroblastoma patients rather than exploring specifically patients with high-risk neuroblastoma (HR-NB). As outlined below, our intention is to focus the analyses on patients aged ≥18 months at diagnosis with metastatic disease, or localized MYCN amplified tumours since this group makes up the majority of patients with HR-NB, but excludes patients aged 12-18 months with metastatic disease who likely have better outcomes and potentially different biology.

The central hypothesis is that factors present at original diagnosis (as well as time to relapse) can predict outcome post-relapse for patients with high-risk metastatic disease (acknowledging that there are additional factors such as therapy post-relapse and nature of the relapse that are beyond the scope of INRG data).

Patient Cohort (Eligibility Criteria):

All patients registered in the INRG database who meet the following criteria:

1. Aged ≥547 days at diagnosis
2. Stage 4 disease or stage 2 or 3 with MYCN amplified tumour
3. Diagnosed 1990 or later
4. Experienced relapse/recurrence

Patients with non-MNA localized tumours with unfavorable histology that may (or may not) have been treated as high-risk will be excluded.

Background:

There have been a number of analyses of factors predictive of survival after relapse of neuroblastoma. The analysis of INRG data was published in 2011 [2] and examined all relapses, including in patients who were not initially identified as having high-risk disease – for example 27% of the cohort was <18 months of age at initial diagnosis. The analysis reported time from diagnosis to first relapse (TTFR), age, stage and MYCN amplification status as predictive of post-relapse OS. As outlined above the aim of the current INRG proposal will to look specifically at a more limited population of patients initially defined as having HR-NB and to undertake a similar analysis but within this more focussed population. Whilst the majority of relapses will occur in patients who were initially high-risk, the implications of neuroblastoma recurrence are very different for low/intermediate compared to high-risk patients and therefore an analysis limited to a more tightly defined group of HR-NB patients may provide information more readily translatable into the design of clinical trials. A number of analyses of relapsed neuroblastoma based on national population cohorts have also been published [3,4]. The planned analysis will also explore changes in survival post-relapse as a function of year of diagnosis (i.e. treatment era) and build on previously published data on changes in overall outcomes for patients with HR-NB [5].

Significance:

A significant proportion of HR-NB patients will relapse and survival after relapse has historically been very poor [6]. Existing published data on survival post-relapse are now out of date (previous analysis [2] only included patients diagnosed up to 2002) and need to be updated with patients treated in a more contemporary era. Analysis specifically of HR-NB patients may identify risk factors for survival post-relapse that were not apparent in the original exploration that focused on all neuroblastoma relapses.

Proposal description:

1. Kaplan-Meier curve of survival post-relapse for whole population
2. Explore differences in survival post-relapse based on year of diagnosis
3. Univariate analyses of potential factors to predict survival post-relapse (this will likely need to be done separately for localized and metastatic patients): age, stage (localized vs metastatic), MYCN status (within metastatic patients only), segmental chromosomal abnormalities, number of metastatic sites involved,

primary site, involvement of specific metastatic sites, serum LDH/ferritin, MKI, histology, treatment allocation, time to first relapse

4. Develop multivariable models incorporating factors shown to be significant in univariate analyses (again likely need to be done separately for localized and metastatic patients)

Data Requested:

For patients meeting inclusion criteria, all available data from within INRG core dataset.

- Age at diagnosis
- Date of diagnosis
- Time to event/last contact
- Event censoring indicator
- Time to death/last contact
- Death censoring indicator
- Serum ferritin and LDH at diagnosis
- Histological classification of primary tumour, MKI, and grade
- Tumour biology: MYCN status, ploidy, 11q, 1p and 17q status
- Location of primary
- Involvement of specific metastatic sites
- Treatment approach

If possible depending on available data, we would also like to look at incorporating genetic risk factors based on available tumour sequencing data into the mutlivariable analysis. We would welcome the opportunity to discuss possibilities in more detail if the project is approved to move forward.

References

1. Cohn SL, Pearson ADJ, London WB, Monclair T, Ambros PF, Brodeur GM, Faldum A, Hero B, Iehara T, Machin D, Mosseri V, Simon T, Garaventa A, Castel V, Matthay KK, INRG Task Force. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. Journal of Clinical Oncology. 2009 Jan 9;27(2):289–97.

2. London WB, Castel V, Monclair T, Ambros PF, Pearson ADJ, Cohn SL, Berthold F, Nakagawara A, Ladenstein RL, Iehara T, Matthay KK. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project. Journal of Clinical Oncology. 2011 Aug 20;29(24):3286–92.

3. Moreno L, Rubie H, Varo A, Le Deley M-C, Amoroso L, Chevance A, Garaventa A, Gambart M, Bautista F, Valteau-Couanet D, Geoerger B, Vassal G, Paoletti X, Pearson ADJ. Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. Pediatric Blood & Cancer. 2017 Jan;64(1):25–31.

4. Basta NO, Halliday GC, Makin G, Birch J, Feltbower R, Bown N, Elliot M, Moreno L, Barone G, Pearson AD, James PW, Tweddle DA, McNally RJ. Factors associated

with recurrence and survival length following relapse in patients with neuroblastoma. Br J Cancer. 2016 Oct 4.

5. Moroz V, Machin D, Faldum A, Hero B, Iehara T, Mosseri V, Ladenstein R, De Bernardi B, Rubie H, Berthold F, Matthay KK, Monclair T, Ambros PF, Pearson ADJ, Cohn SL, London WB. Changes over three decades in outcome and the prognostic influence of age-at-diagnosis in young patients with neuroblastoma: A report from the International Neuroblastoma Risk Group Project. Eur J Cancer. Elsevier Ltd; 2011 Mar 1;47(4):561–71.

6. Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, Casale F, Viscardi E, Bianchi M, D'Angelo P, Zanazzo GA, Luksch R, Favre C, Tamburini A, Haupt R. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer. 2009 Nov 1;45(16):2835–42.