European Journal of Cancer (2013) 49, 3671–3679

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

Treatment of children over the age of one year with unresectable localised neuroblastoma without *MYCN* amplification: Results of the SIOPEN study

J.A. Kohler [a], H. Rubie [b], V. Castel [c,p], K. Beiske [d,o], K. Holmes [e], C. Gambini [f,o], F. Casale [g], C. Munzer [b], G. Erminio [h], S. Parodi [h], S. Navarro [i,o], C. Marquez [j], M. Peuchmaur [k,o], C. Cullinane [l], P. Brock [m], D. Valteau-Couanet [n] A. Garaventa [h,*], R. Haupt [h]

[a] *Department of Paediatric Oncology, Southampton General Hospital, Southampton, UK*
[b] *Unité d'Hémato-Oncologie, Hôpital des Enfants, Toulouse, France*
[c] *Pediatric Oncology Unit, Hospital Universitario La Fe, Valencia, Spain*
[d] *Department of Pathology, Oslo University Hospital Rikshospitalet, Oslo, Norway*
[e] *Department of Paediatric Surgery, St. George's Hospital, London, UK*
[f] *Department of Pathology, Istituto G. Gaslini, Genova, Italy*
[g] *Department of Pediatric Oncology, Seconda Università degli Studi di Napoli, Napoli, Italy*
[h] *Epidemiology, Biostatistics and Committees Unit, Istituto G. Gaslini, Genova, Italy*
[i] *Departamento de Patología, Facultad de Medicina, Valencia, Spain*
[j] *Unidad de Oncología Pediátrica, Hospital Infantil Virgen del Rocío, Sevilla, Spain*
[k] *Département d'Anatomie et Cytologie Pathologiques, Hôpital Robert Debre, Paris, France*
[l] *Department of Histopathology, St. James University Hospital, Leeds, UK*
[m] *Department of Paediatric Hematology-Oncology, Great Ormond Street Hospital, London, UK*
[n] *Département d'Oncologie Pédiatrique, Institut de cancérologie Gustave Roussy, Paris, France*

Available online 29 July 2013

KEYWORDS
Children
Conventional chemotherapy

Abstract ***Background:*** In children older than 1 year with localised unresectable neuroblastoma (NB), treatment strategies are heterogeneous according to the national groups. The objective of this phase III non-randomised study was to evaluate the efficacy of conventional chemotherapy followed by surgery.

* *Corresponding author:* Address: Department of Hematology Oncology, Giannina Gaslini Children's Hospital, Largo Gaslini, 5 - 16147 Genova, Italy. Tel.: +39 0105636 694; fax: +39 010 5636 714.
E-mail address: albertogaraventa@ospedale-gaslini.ge.it (A. Garaventa).

[o] K.B., C.G., S.N. and M.P. represent the SIOPEN Pathology review panel comprising Drs. Gabriele Amann, University Clinic of Pathology, Vienna, Austria; Klaus Beiske, Department of Pathology, Oslo University Hospital Oslo, Norway; Catherine Cullinane, Royal Manchester Children's Hospital, Manchester, UK; Emanuele D'Amore, UO di Anatomia Patologica, Ospedale S. Bortolo, Vicenza, Italy; Claudio Gambini, Department of Pathology, Istituto G. Gaslini, Genova, Italy; Samuel Navarro, Departamento de Patología, Facultad de Medicina, Valencia, Spain and Michel Peuchmaur, Service de Pathologie, Hôpital Robert Debré, Université Paris, Paris, France.

[p] V.C. supported by grant FIS.PS 09/02323.

http://dx.doi.org/10.1016/j.ejca.2013.07.002

Localised neuroblastoma
Unresectable

Patients and methods: In the presence of surgical risk factors (SRF), six courses of chemotherapy alternating Carboplatin–Etoposide and Vincristin–Cyclophosphamide–Doxorubicin were given, and surgical resection was attempted after four. Survival analyses were performed using an intention-to-treat approach. The main objective was to achieve a 5-year survival over 80%.
Results: Out of 191 registered children, 160 were evaluable. There were 62.5% older than 18 months and 52.5% had unfavourable histology according to International Neuroblastoma Pathology Classification (INPC). Chemotherapy reduced the number of SRFs by one third. Delayed surgery was attempted in 86.3% of patients and was complete or nearly complete in 74%. The 5-year EFS and OS were 76.4% and 87.6% respectively, with significant better results for patients younger than 18 months or with favourable histology.
Conclusion: This strategy provides encouraging results in children older than 1 year or 12 months with localised unresectable NB without MYCN amplification. However, in children older than 18 months and with unfavourable histology, additional treatment is recommended.

1. Introduction

Although age and stage at diagnosis are traditionally the most important prognostic factors in children with neuroblastoma (NB), a number of studies have demonstrated the importance of biological factors, especially amplification of the *MYCN* gene.[1,2] For children with localised disease, without MYCN amplification, gross surgical excision is considered the main requirement for cure, and this was confirmed in the recent European study Localised Neuroblastoma European Group (LNESG)-1.[3] However localised but unresectable NB carries a poorer prognosis except in infants[4–6] or in children with favourable biological features.[7–9] For children older than 1 year, although some groups reported encouraging results after primary surgery without cytotoxic treatment,[10] most cooperative groups have emphasised the need for primary chemotherapy, including high-dose chemotherapy (HDC), followed by delayed surgery[11–16] and sometimes local radiotherapy.[17,18]

In the present study, if operation was considered hazardous, children with unresectable localised NB were to receive conventional chemotherapy, before an attempt at surgical resection. This represented a reduction of the burden of treatment for most teams as compared to previous European national strategies.[12,14,15] No radiotherapy was recommended irrespective of response or residual disease. The objective of this study was to confirm the efficacy of such a strategy in a large multinational setting in children older than 1 year with a tumour deemed unresectable and without MYCN amplification.

2. Patients and methods

2.1. Eligibility

All consecutive and previously untreated children older than 1 year with clinical and imaging data suggesting an unresectable localised NB were included in the study. Initial work up included measurement of urinary catecholamine metabolites, serum ferritin and lactate dehydrogenase (LDH) levels and imaging of the primary tumour (computed tomography (CT) scan and/or magnetic resonance imaging (MRI)). Since tumour resection may be operator-dependant, the International Society of Paediatric Oncology (SIOPEN) group has defined 'surgical risk factors' (SRF), based on pre-operative imaging, which reduce the probability of complete resection and/or imply an increased risk of surgery-related complications.[19] SRF are defined for each tumour localisation and in general exist when the tumour encases or invades a vital structure, most commonly a major blood vessel.[19,20] These factors have been subsequently adopted by the International Neuroblastoma Risk Group (INRG) and are termed Image Defined Risk Factors or IDRFs.[21]

As a rule, patient imaging was to be discussed by the multidisciplinary teams of the participating centres with the aim to identify and register the SRF, without assigning them a score. Chemotherapy administered prior to the attempt at surgical removal was intended to reduce the SRF, by reducing tumor volume and vascularity, and thus limit excessive bleeding and risk of damaging vital structures surrounding the tumour.

Children with resectable tumour but with contralateral positive nodes were also included into the study (International Neuroblastoma Staging System (INSS) stage 3 resected). Histological confirmation of NB and MYCN status was mandatory and done by biopsy. Tumour samples were centrally and retrospectively reviewed by a panel made of the national reference pathologists and classified according to International Neuroblastoma Pathology Classification (INPC) guidelines.[22,23] MYCN status was analysed according to the European Neuroblastoma Quality Control Assessment (ENQUA)[24] approved national Reference Centres, and only children with a non-*MYCN* amplified tumour were eligible for this study. Patient's age, histology and Mitosis-Karyorrhexis Index (MKI) defined the favourable or unfavourable category according to INPC. Metastatic