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Survival outcome of intermediate risk neuroblastoma at Children Cancer Hospital Egypt

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ABSTRACT

Aim: The study aims to evaluate survival outcome in newly diagnosed pediatric intermediate risk neuroblastoma patients treated at the Children Cancer Hospital – Egypt and their relation to various clinical and pathological factors.

Methods: The study included stage 3 patients <1.5 years, children 1.5 years or older with stage 3 disease and favorable histopathological features, infants (<1 year) with International Neuroblastoma Staging System (INSS) stage 4 disease, stage 4 children 1–1.5 years with favorable biology, and infants stage 4 s (with unfavorable biologic features). Patients received systemic chemotherapy, in the form of etoposide and carboplatin alternating with cyclophosphamide, doxorubicin and vincristine, administered at 3-week intervals, with a total of 6 or 8 cycles guided by reaching objective overall response (complete/very good partial/partial response).

Results: The study included 136 patients, 67 males and 69 females. 101 patients had abdominal primary tumors, 28 had mediastinal masss and 7 with masses in the neck; 68% were stage 3 and the remaining (n = 44) had metastatic disease.

The three-year overall survival (OS) and event-free survival (EFS) estimates were 94% ± 2% and 90.9% ± 2.5%, respectively. OS and EFS by gender, age, pathology and INPC were all statistically not significantly different. Moreover, OS for patients having surgery versus no surgery (inoperable residual only) was statistically significant (98.4% ± 1.6% & 88.7% ± 5.3%, respectively, p = .034).

Conclusion: A very high rate of survival is currently achievable in patients with intermediate risk neuroblastoma by chemotherapy or chemotherapy and surgery. In addition to response, our plan is to adopt biologically-based treatment to reduce treatment-induced complications among survivors.

Introduction

Neuroblastoma (NB) is the most common pediatric extracranial malignant solid tumor and of neural crest origin. It most commonly arises in the adrenal medulla or along paraspinal sites, where sympathetic nervous system tissue originates.

Neuroblastoma is remarkable for its broad spectrum of clinical behavior, ranging from spontaneous regression to inevitable progression and death [1]. Less than 40% of children, older than 12 months with metastatic disease at diagnosis, survive, despite multimodality treatment that includes stem-cell transplantation. This clinical diversity correlates closely with numerous clinical and biological factors, including patient age, tumor stage, tumor histology,

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and genetic abnormalities. Identification of risk groups on the basis of clinical and molecular prognostic variables has allowed tailoring of therapy to improve outcomes and minimize the risk of deleterious consequences of therapy.

Children's Oncology Group (COG) established a system of risk stratification for NB in 1998. This stratification was based on clinical data, including patient age at diagnosis and tumor stage, and tumor-derived biologic data, including histopathological classification, status of *MYCN* oncogene amplification, and DNA ploidy. Survival proportions of pediatric NB have been markedly improved after development of risk stratification system that favored multimodality tailored treatment [2].

This study aims to evaluate survival outcome [overall (OS) and event-free survival (EFS)] in newly diagnosed pediatric IR NB patients treated at the Children Cancer Hospital – Egypt (CCHE) and their relation to various clinical and pathological factors.

Patients and methods

This retrospective study included all newly diagnosed patients at CCHE with IR NB during the period from January 2011 till December 2014; patients enrolled are below 18 years of age with no prior chemotherapy or radiotherapy.

Before starting therapy, approval of this treatment plan by institutional review board was obtained. Informed consent was also retrieved before enrollment of patients on this protocol according to CCHE guidelines.

Diagnosis

Medical history, physical examination, laboratory and radiological data were systematically reviewed for all patients. Laboratory investigations with serum concentrations of neuron-specific enolase (NSE), ferritin, lactate dehydrogenase (LDH) and urinary vanillylmandelic acid (VMA) were done. Pathological studies were available. A pre-treatment biopsy of the primary tumor was mandatory. Tissue samples obtained through true cut needle biopsy or open biopsy, if inadequate. Measurement of MYCN gene amplification was carried out by fluorescent in situ hybridization (in paraffin blocks) on the primary tumor at time of diagnosis.

Before each cycle of chemotherapy, all patients had evaluations of renal, hepatic, and hematologic function. Echocardiogram was performed for patients prior to each cycle containing doxorubicin and after completion of treatment.

Staging & risk stratification

Initial assessment of the primary tumor was done by CT/MRI scan. Systemic evaluations were conducted for possible metastatic sites including, bilateral bone marrow aspirate/biopsy, bone scan (Technetium 99 m-methyldiphosphonate) and Iodine-131 metaiodobenzylguanidine (MIBG) scan (if available). Clinical variables including patient's age and stage were used in association with pathological features (INPC histopathology classification and MYCN status) in determining patients with IR NB. All IR NB patients were required to have nonamplified MYCN status. IR included stage 3 patients <1.5 years of age, children 1.5 years or older with stage 3 disease and favorable histopathological features, infants (younger than 1 year of age) with International Neuroblastoma Staging System (INSS) stage 4 disease, stage 4 children 1–1.5 years of age with favorable histology and hyperploidy, and infants with stage 4 s disease (with unfavorable biologic features: unfavorable histology and diploidy) [3].

Treatment

Patients received systemic chemotherapy, in the form of etoposide and carboplatin (VP16/CARBO) alternating with cyclophosphamide, doxorubicin and vincristine (CADO), administered at 3-week intervals, with total of 6 or 8 cycles guided by attaining objective overall response [complete response (CR)/very good partial response (VGPR)/partial response (PR)]. Evaluation was done after 4 cycles; if patient reached at least PR, 2 more cycles were given as consolidation; if patient did not reach objective response after 4 cycles, he was given 2 to 4 more cycles aiming at reaching objective response (reassessment was done after 6 cycles, if patient still did not reach at least PR, then patient is to complete a maximum of 8 cycles with final assessment afterwards).

VP16/CARBO

Etoposide: 200 mg/m^2/day (6.67 mg/kg/day for patients $\leq$12 kg) infused IV over 2 h $\times$ 3 days.

Carboplatin: 450 mg/m^2/day (15 mg/kg/day for patients $\leq$12 kg) infused IV over 1 h on day 1.

CADO

cyclophosphamide: 300 mg/m^2/day (10 mg/kg/day for patients $\leq$12 kg) Infused IV over 1 h daily for 5 days.

Doxorubicin: 60 mg/m^2/day (2 mg/kg/day for patients $\leq$12 kg) infused IV over 6 h on day 5.

Vincristine: 1.5 mg/m^2/day (0.05 mg/kg/day for patients $\leq$12 kg) IV bolus days 1 and 5 (maximum dose 2 mg).

Timing for local surgical control of post-induction residual tumor was according to tumor response after 4 cycles (induction) whenever safely feasible. Surgery was attempted 2–3 weeks from end of last administered cycle. Surgery was omitted for patients with no/minimal residual disease and for patients with inoperable residual.

Response evaluation

According to International Neuroblastoma Response Criteria (INRC), response evaluation was done post induction chemotherapy, after local control, and at regular checkpoints (cycle 6 and at end of treatment) thereafter by radiological imaging and by bone marrow biopsy/aspirate (if previously positive or suspected infiltration on MIBG scanning).

CR: complete tumor disappearance; VGPR: decrease in primary tumor volume by 90–99 %. PR: 50% to less than 90% decrease in primary tumor volume compared to the measurement obtained at study enrollment. Progressive Disease (PD): Any new lesion, increase of any measurable lesion by <25% or previous negative marrow became positive for tumor. Stable disease (SD): No new lesion, <50% reduction but <25% increase in any existing lesion [4].

Statistical analysis

Medical records were used for retrieving data that were eligible for analysis.

Data management was done using REDCap (Research Electronic Data Capture) tool hosted at CCHE after placement of an in-house developed software. All statistical calculations were done using SPSS (Statistical Package for the Social Science; IBM, USA) version 20 for Microsoft Windows.

Quantitative data were expressed as median and range, qualitative data were expressed as frequency and percentage.

Overall and event-free survivals (OS, EFS) were estimated by Kaplan Meier; comparison was done using log-rank test. For EFS, time to event was defined as time from enrollment on protocol till

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