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Journal of the Egyptian National Cancer Institute (2011) **23**, 47–53

Cairo University

Journal of the Egyptian National Cancer Institute

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ORIGINAL ARTICLE

Did salvage ICE chemotherapy improve the outcome in primary resistant/relapsing stage III/IV neuroblastoma?

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Received 10 November 2010; accepted 9 February 2011
Available online 7 September 2011

KEYWORDS

Neuroblastoma;
ICE;
Salvage chemotherapy

Abstract *Background and purpose:* Neuroblastoma is the most common extracranial and deadly solid tumor in children. It accounts for 15% of the deaths from cancer in the pediatric age group. Approximately half of the newly diagnosed children are at "high risk" of treatment failure.
The aim of this study is to evaluate the response rate of salvage chemotherapy by the ICE (Ifosfamide, Carboplatin, and Etoposide) regimen when administered to previously treated primary refractory or progressive high risk neuroblastoma patients.
Patients and methods: Sixty-six patients from the National Cancer Institute (NCI), Cairo University and the Children Cancer Hospital Egypt (CCHE) received salvage chemotherapy (ICE) either

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doi:10.1016/j.jnci.2011.07.007

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due to primary resistance in 51/66 (77.2%) or due to disease progression on primary chemotherapy in 15/66 (22.8%).

Results: They were 40 males (60.6%) and 26 females (39.4%). Patients' age ranged between 3 months and 12.5 years. The most common tumor site was suprarenal, followed by retroperitoneal mass. Two patients (3%) died from chemotherapy toxicity during ICE administration. Evaluation of tumor response in the remaining 64 patients showed the following: CR/PR in 24 patients (36.5%), SD in 11 patients (16.6%), and PD in 29 patients (43.9%).

Fourteen patients (21.2%) were considered eligible for auto BMT, while 50/64 patients (78.8%) failed this second line (salvage) chemotherapy and had palliative lines of therapy.

By the end of the study (May 2010), 47/66 (71.2%) of the patients were still alive, while 19/66 (28.8%) were dead. Two out of 14 patients (14.2%) who underwent HSCT died from post transplantation disease progression, while 12/14 (85.8%) were in CCR.

Conclusion: Chemotherapy by ICE for primary resistant or progressive stage III/IV NB seems well tolerated. With a 36.6% response rate, 18% CCR, and 3% treatment mortality rate, it could be considered a good salvage therapy in the category of patients who are condemned for palliation.

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Introduction

Neuroblastoma (NB) is the most common extracranial and deadly solid tumor in children. It accounts for 8–10% of childhood cancers and 15% of the deaths from cancer in the pediatric age group [1]. Approximately half of the newly diagnosed children with this tumor will have metastatic disease or histologically aggressive large tumors that are at ''high risk'' for treatment failure [2].

Several prognostic factors have been identified including age, staging system, but the amplification of N-MYC confers a worse prognosis for all neuroblastic tumor groups, including patients with locoregional tumors or young infants [3,4].

Approximately 80% of stage IV patients have detectable marrow involvement. Similarly, patients with multiple bone metastases had a worse outcome. Overall, patients with abdominal primaries in particular stages III and IV, have a less favorable prognosis than those with cervical, pelvic, and thoracic primaries [5].

Chemotherapy is still the mainstay treatment for the systemic control of these tumors. Currently, the most common chemotherapeutic agents utilized are cyclophosphamide, iphosphamide, vincristine, doxorubicin, cisplatin, Carboplatin, Etoposide and melphalan [6].

Over the last two decades several new chemotherapeutic agents with anti-neuroblastoma activity have been studied including irinotican, topotecan, cyclophosphamide and temozolamide [6]. For advanced-stage tumors, combined chemotherapy failed to effectively eradicate the disease; however, it often reduces the size of the primary tumors of advanced stage, allowing them to be resectable [7].

Bone marrow-ablative therapy with total body irradiation or melphalan with subsequent bone marrow transplant (BMT) has shown to improve event-free survival as compared to intensive chemotherapy for high-risk neuroblastoma patients [8,9].

Notwithstanding the intensive treatment, relapse and refractory disease are frequent and still pose a clinical challenge, as long-term survival after relapse is virtually unheard of [10].

Current surgery and radiotherapy techniques in conjunction with induction chemotherapy have greatly reduced the risk of local relapse. However, in advanced neuroblastoma, circulating tumor cells were detected in the peripheral blood by several methods, suggesting that advanced disease is no longer localized.

The clinical significance of intensive surgical therapy as a means to control the local lesion has been controversial in the treatment of advanced neuroblastoma to date. Therefore, the role of extensive surgery with a higher incidence of major complications was not supported in some reports [11,12], but emphasized in one study [13].

Total surgical resection with Intra-Operative Radiotherapy (IORT) is considered to be the most intensive surgical therapy to control the local malignant lesion, because the electron beam of IORT is estimated to reach to the depth of 1 cm into the tissue and eliminate the viable tumor cells [14,15].

The aim of this study is to evaluate the response rate of salvage chemotherapy by the ICE (Ifosfamide, Carboplatin, and Etoposide) regimen when administered to previously treated primary refractory or progressive high risk neuroblastoma patients.

Patients and methods

Patients with stages III/IV neuroblastoma who were either primary refractory or progressive on high risk treatment protocol were included in this study. They were treated at the Pediatric Oncology Department either at the Egyptian National Cancer Institute (NCI), Cairo University, or the Children Cancer Hospital Egypt (CCHE) during the period from July 2007 to December 2009, with a follow up period until May 2010.

Patients received from 2 to 8 courses of salvage chemotherapy ICE (Ifosfamide 1.8 g/m^2 day 1–5, Carboplatine 450 mg/m^2 day 1 and Etoposide 100 mg/m^2 day 1–5) aiming to achieve CR/PR and, subsequently go to consolidation with intensive dose chemotherapy and Hematopoietic Stem Cell Transplantation (HSCT).

Patient eligibility

A. Patients received high risk induction chemotherapy if they had:
   1. Biopsy-proven neuroblastoma or positively infiltrated bone marrow.
   2. Age of patients less than 18 years at diagnosis.
   3. Staging:
      - Stage IV patients except those less than 1 year of age with non-amplified N-MYC gene.
      - Stage III patients with amplified N-MYC gene.
      - Stage III patients with unfavorable Shimada pathology.
   4. Adequate hematopoietic, hepatic and renal functions.

Pathology guidelines

Cases were histologically evaluated according to the International Neuroblastoma Pathology Committee, Shimada 1999 taking into consideration age, histologic picture and the Mitosis Karyorrhexis index for stratification of patients into favorable and unfavorable. N-MYC gene status was performed using Fluorescence In Situ Hybridization (FISH) on paraffin embedded tissue sections.

Definition of response criteria

Complete response (CR). Complete disappearance of all measurable or evaluable lesions (except bone).

Partial response (PR). Reduction (20–99%) in the product of the two largest diameters (perpendicular) of measurable lesions.

No response (NR) or stable disease (SD). Tumor reduction ($<20\%$) of the product of the two largest diameters (perpendicular) of measurable lesions.

Progressive disease (PD). $>25\%$ increase in the product of the two largest diameters (perpendicular) of measurable lesions.

Relapse. Recurrence of disease at any site after achieving a CR.

Primary chemotherapy

Patients received induction chemotherapy with eight cycles of alternating VP16/CARBO [Etoposide $200\ mg/m^2 \times 3$ days and Carboplatin $500\ mg/m^2$ on day 1] and CADO [cyclophosphamide $300\ mg/m^2 \times 5$ days, doxorubicin $60\ mg/m^2$ day 5 and vincristine $1.5\ mg/m^2$ (maximum 2 mg) days 1 and 5].

B. Patients were eligible for salvage ICE chemotherapy if they had:

Failure of induction chemotherapy as evidenced by either primary refractory (failure to achieve CR/PR after 4–6 cycles of Induction chemotherapy), or progressive disease with adequate hematopoietic, hepatic and renal functions.

Patient evaluation

The following work-up was done before starting salvage chemotherapy:

(1) CT scan of the primary tumor and all metastatic sites.
(2) Bilateral bone marrow aspirate and biopsy.
(3) Whole Body Tc99 Bone scan.
(4) MIBG scan (when feasible).

Salvage chemotherapy

Two to eight cycles of ICE were given, aiming to achieve CR/PR for primary refractory, relapsing, or progressive disease in NB patients.

Reassessment of tumor response was performed after every second course by CT/MRI, bone scan, MIBG scan, and BM biopsy (if previously positive or suspected infiltration on MIBG scanning).

Patients with CR/VGPR were assessed for operability (if their tumor was not previously resected), followed by HSCT and involved field (IF) radiotherapy. Those with partial response or stable disease resumed chemotherapy till they became eligible for HSCT, or reached a maximum of eight courses. Patients with disease progression were taken off therapy.

Surgical guidelines

The goal of this surgery was gross total resection of residual tumor in the primary site as well as tumor in areas of regional dissemination (usually lymph nodes). Resection with microscopically negative margins may not be feasible because of proximity to major vascular structures and the spine. Timing for surgical interference was determined according to tumor response at different stages of therapy.

Radiotherapy guidelines

Local irradiation was administered to the primary site in patients after HSCT. The macroscopic tumor volume (GTV) was defined from post induction chemotherapy scans that were obtained prior to the time of delayed surgical resection. The clinical target volume (CTV) was defined as the GTV plus a 1.5-cm margin. The planning target volume (PTV) was defined as the CTV plus a 0.5 cm margin. For patients without evidence of macroscopic residual disease after induction chemotherapy and surgical resection, a dose of 21.6 grays (GY) was administered in 1.8 Gy fractions per day 5 days a week. Areas of macroscopic residual disease after surgery received an additional booster dose of 14.4 Gy over eight fractions, for a total dose of 36.0 Gy. Radiation was also given to metastatic sites with persistent active disease on MIBG and/or bone scan demonstrated on the pre-HSCT evaluation. The planning target volume for metastatic sites is the area of residual tumor defined on MIBG, CT or MR scan with a 1 cm margin.

Statistical analysis

SPSS package for Windows, version 15 (SPSS Inc., Chicago, Illinois, USA) was used. The overall survival was calculated from the date of diagnosis to the date of death or of last contact. The functions for overall survival were estimated using the Kaplan–Meier product limit method [16]. Comparison between two survival times was done by the Log-rank test. p-Value equal to or less than 0.05 was considered significant.

Results

Sixty-six patients were eligible for the study. Table 1 shows patients' characteristics at presentation.

Patients' age ranged between 3 months and 12.5 years with a median of 3.3 years.

According to the International Neuroblastoma Staging System (INSS), most of the patients were in stage IV. The most common tumor site was suprarenal.

Following induction chemotherapy, 41/66 patients (62.1%) had surgical intervention as a form of local therapy, while 25/66 patients (37.9%) were not eligible for surgical resection mostly due to tumor irresectability. Twenty patients (30.3%) received radiotherapy to the primary or metastatic site of the tumor, 11/66 of them (16.6%) post autologous HSCT, and 9/66 patients (13.6%) on palliative basis. The rest of the patients (46/66 patients, 70%) were not eligible for radiation therapy.

Causes of salvage chemotherapy by ICE were either primary resistant in 51/66 (77.2%) or disease progression in 15/66 (22.8%).

Two patients (3%) died from chemotherapy toxicity during ICE administration. Evaluation of tumor response in the remaining 64 patients at the end of the study [May 2010] showed the following: CR/PR in 24 patients (36.5%), SD in 11 patients (16.6%), PD in 29 patients (43.9%) by the end of the chemotherapy course (6 months).

Fourteen patients (21.2%) were considered eligible for HSCT, while 50/64 patients (78.8%) failed this second line (salvage) chemotherapy and had palliative lines of therapy.

Patients who underwent HSCT were eight males and six females. Their ages ranged from 9 months to 9.8 years, and the median age was 3.4 years. Almost all the patients 13/14 (92.8%) had neuroblastoma while 1/14 (7.2%) patients had ganglioneuroblastoma. Shimada classification was favorable in 4/14 (28.5%) and unfavorable in 10/14 (71.5%). According to INSS; 3/14 (21.4%) patients had stage III while 11/14 (78.5%) patients had stage IV disease. Eleven patients (78.5%) had suprarenal mass, 2/14 (14.3%) had retroperitoneal mass and 1/14 (7.2%) had a mediastinal mass.

Table 1 Patient characteristics at presentation.

	Total number (n = 66)	Percentage
Sex		
Male	40	60.6
Female	26	39.4
Pathology		
Favorable	10	15.2
Unfavorable	56	84.8
N-Myc		
Amplified	16	24.2
Nonamplified	23	34.8
Not done	27	40.9
Stage		
3	10	15.2
4	56	84.8
Site		
Suprarenal	44	66.6
Retroperitoneal	10	15.2
Mediastinal	6	9.1
Other sites	6	9.1
Surgery	41	62.1
Radiotherapy	20	30.3

Surgical intervention (either initially or following ICE) was done for 11/14 (78.5%) while 3/14 (21.4%) patients underwent HSCT without being operated upon due to tumor irresectability. The type of surgery was complete resection in 10/11 (90.9%) and partial resection (debulking) in 1/11 (9.1%). Most of the good responding patients (12/14 85.7%) were initially primary resistant while 2/14 (14.2%) received salvage therapy due to disease progression. ICE cycles given for BMT patients were of a minimum of two cycles and a maximum of six cycles (median four cycles).

Post HSCT, 11 patients (78.5%) received a radiation of 21.6 Gy to the operative bed. One patient required an additional boost dose of 14.4 Gy over eight fractions, for a total dose of 36.0 Gy. Of the three patients who did not receive radiation, two patients died from post transplantation disease progression and one patient's family declined the option to receive radiation.

By the end of the study (May 2010), 47/66 (71%) of the patients were still alive, while 19 patients (29%) were dead.

Twelve patients (18%) were in continuous complete remission (CCR) post HSCT, while 35/66 (53%) were alive in disease progression under palliative measures.

Two patients (3%) died from chemotherapy [ICE] toxicity, two of the patients (3%) who underwent HSCT and 15/66 (23%) of the nonresponders died from disease progression.

The median follow up time was 18 months and ranged from 1.4 to 33.2 months. The cumulative overall survival at 33.2 months was 68% (Fig. 1).

The cumulative overall survival stratified by initial disease status at 18 months was 65% for those with progressive disease, while it was 69% for primary resistant patients at the same time period. This difference was not statistically significant (p-value 0.44) (Fig. 2).

When comparing the survival for those who received HSCT and the rest of the group, cumulative overall survival was 90% and 60%, respectively at 18 months, but this difference was not statistically significant (p-value 0.06) (Fig. 3).

Discussion

In our study, salvage ICE chemotherapy showed CR/PR response of 36.6%, allowing about 21% of the patients to go for auto HSCT, and about 18% to go into CCR. With mainly grade IV hematopoietic toxicity, and 3.8% toxic deaths – in previously heavily treated cancer patients – it seems to be well tolerated.

ICE chemotherapy has been used with success for resistant lymphomas and relapsed solid tumors [5], due to the favorable spectrum of non-hematopoietic toxicity and evidence of synergy in vitro of these selected drugs.

In advanced and recurrent neuroblastoma, Garaventaa et al. achieved CR and PR rate of 73% after 1–8 courses of ICE (median 2) [17].

The camptothecins topotecan [17–19] and irinotecan [20,21] have proven anti-NB activity and have been extensively used in salvage regimens. Until recently the combination of cyclophosphamide and topotecan was the first line salvage regimen

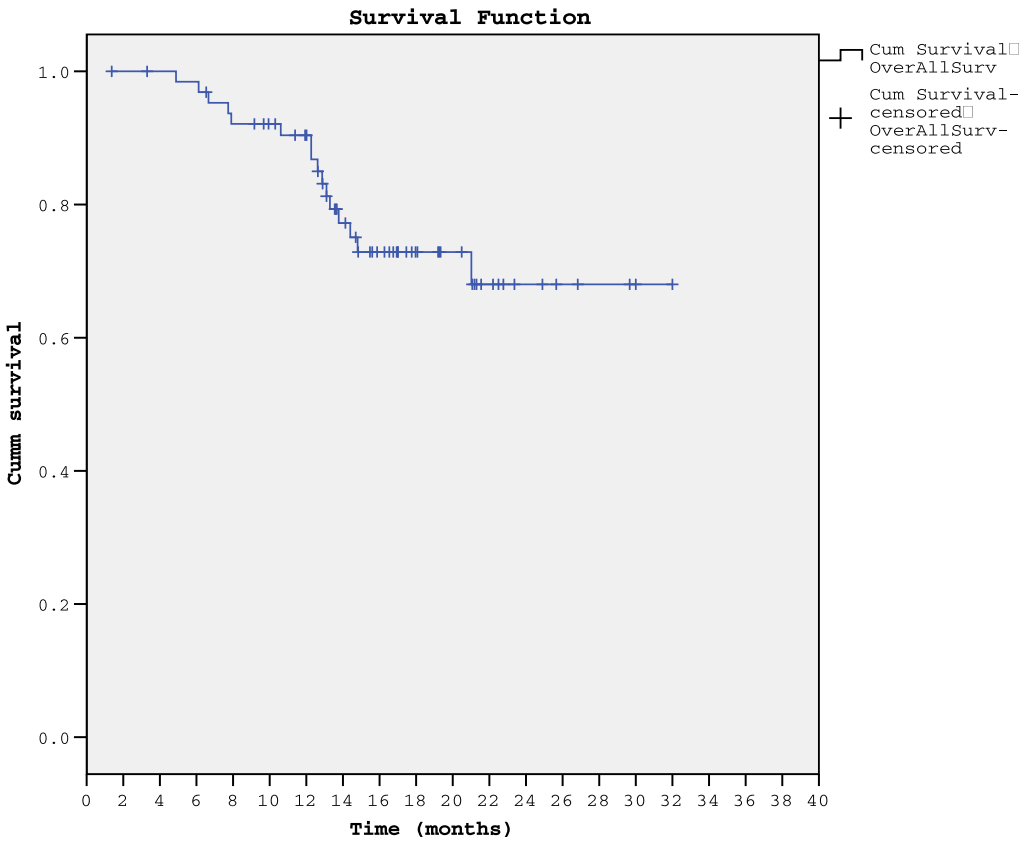
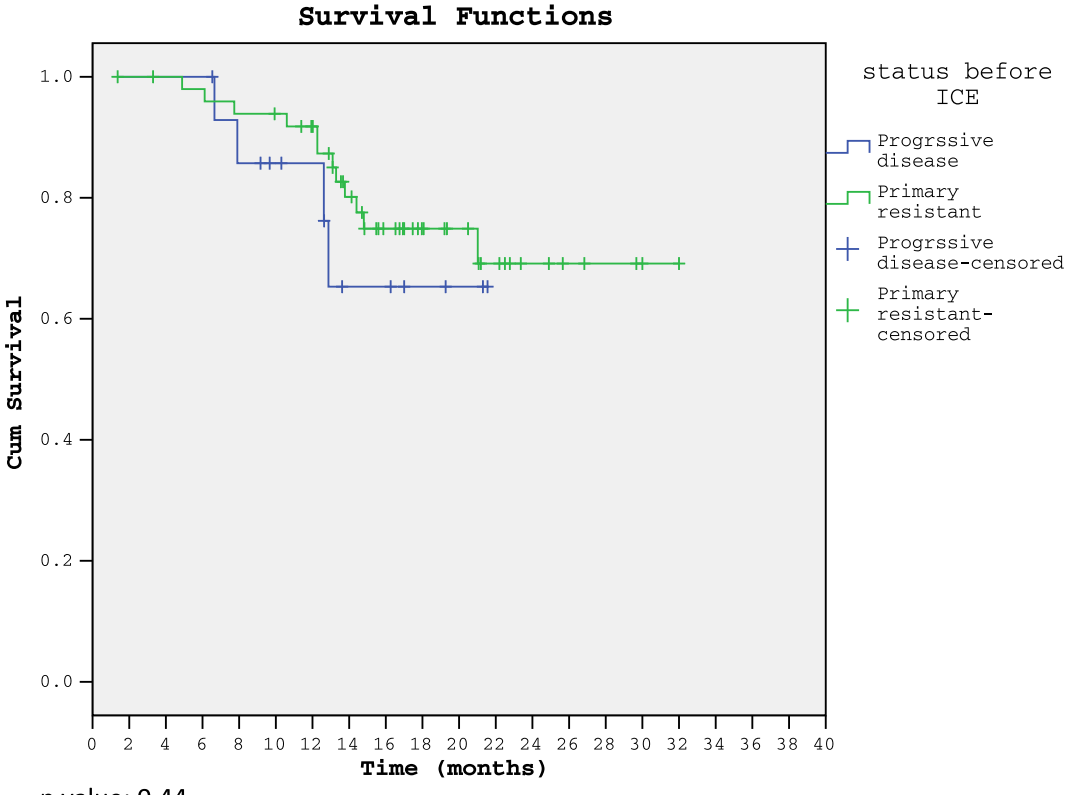


Figure 1 Overall survival for the 66 patients.



p value: 0.44

Figure 2 Overall survival stratified by initial status.

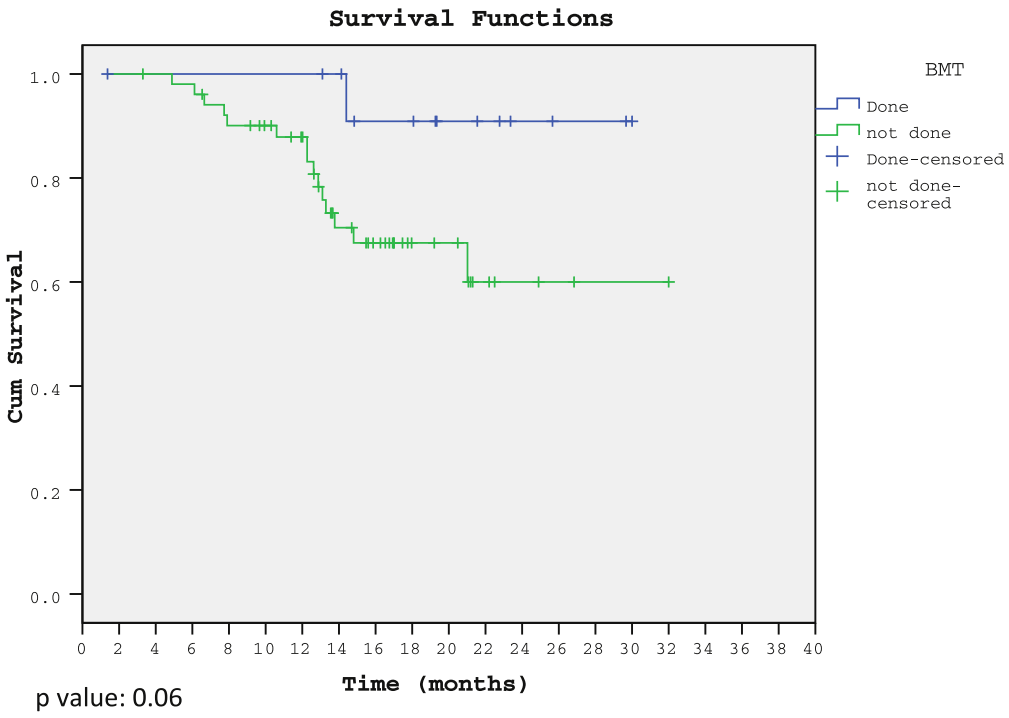


Figure 3 Oified by BMT status.

studied by the COG [22]. With the incorporation of this combination into front line therapy in the current COG protocol for newly diagnosed high-risk NB, it is likely that a further well studied combination of irinotecan plus temozolomide will be increasingly utilized for resistant NB [23]. Both combinations have demonstrated anti-NB utility though CR/VGPR was rare. Irinotecan was evaluated for efficacy and safety in pediatric recurrent or refractory neuroblastoma with no objective response in heavily pre-treated children [24].

In our study, patients received from 2 to 8 courses of ICE (mean 5 and median 3.65). Response rate was 36.6% CR/PR, 13.6% SD, 43.9% PD, and allowing 21% of the good responders to undergo HSCT.

Our CR and PR rate are lower than what Kramer et al. [25] reported in their study to evaluate the role of high dose ICE therapy for advanced, recurrent NB; for 26 evaluable patients, they had 6 CRs, 13 PRs, 2 SDs, and 3 PDs with a CR and PR rate of 73% achieved after 1–8 courses of ICE (median 2), and six responders went onto BMT. They concluded that high dose ICE is an effective, fast acting remission induction therapy for patients with advanced recurrent neuroblastoma. This might be due to the dose of Carboplatine ICE which was escalated in Kramer's study [25].

At Memorial Sloan Kettering Cancer Center (MSKCC), camptothecins are combined with high-dose cyclophosphamide both for anti-NB effect and to permit the administration of the murine antibody 3F8 for consolidation in case of response to chemotherapy [26]. Other new chemotherapeutic agents with potential anti-NB activity include ABT-751, an oral anti-tubulin agent, though no complete or partial responses were observed in the initial phase I study [18].

In our study, patients who achieved CR/PR and went into auto HSCT are those who had favorable Shimada pathology, stage III initial tumor, suprarenal mass and more surgical resection in comparison to the total number of patients (Table 1). Similarly, "The Italian Neuroblastoma Registry" investigated and detected a better overall survival (OS) after progression and relapse for age at diagnosis < 18 months, less advanced International Neuroblastoma Staging System (INSS) stage, normal lactate dehydrogenase (LDH) serum level, normal N-MYC gene status ($p < 0.001$) and a non-abdominal primary site. A local type of recurrence had a significantly better outcome only in case of relapse [17].

Conclusion

Chemotherapy by ICE for primary resistant or progressive stage III/IV NB seems well tolerated. With a 36.6% response rate and an 18% CCR, ICE could be considered a good salvage therapy in a category of patients who are condemned for palliation.

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