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High-dose cyclophosphamide–irinotecan–vincristine for primary refractory neuroblastoma

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ABSTRACT

Background: We used a novel regimen for neuroblastoma (NB) that had responded inadequately to standard chemotherapy which now includes topotecan in induction or second-line therapy.

Patients and methods: We retrospectively studied 38 patients who received one or two courses of high-dose cyclophosphamide (140 mg/kg)-irinotecan (CPT-11) (250 mg/m^2)-vincristine (HD-CCV) as treatment for NB that had responded incompletely to induction but had never progressed. Treatment was outpatient and was preceded and followed by extent-of-disease and toxicity evaluations because the patients were being considered for enrolment on formal protocols. Progression-free survival (PFS) was calculated from day 1 of HD-CCV.

Results: Common toxicities were grade 4 myelosuppression and grade 2 diarrhoea. Responses – 5 complete (CR), 3 partial (PR), 4 mixed (MR) – occurred in 12/28 (43%) patients treated ⩽9 months, and in 1/10 (10%) patients treated >10 months, from diagnosis. HD-CCV was the initial salvage regimen after topotecan-containing induction in 5 patients, achieving 1 CR, 1 MR and 3 stable disease (NR). HD-CCV produced responses (2 PR, 3 MR) in all 5 patients previously treated with CPT-11/ temozolomide. In contrast, all 6 patients treated post-HD-CCV with CPT-11/temozolomide had NR to the latter. Post-HD-CCV treatments included immunotherapy, targeted radiotherapy and/or chemotherapy. PFS was 64% (±8%) at 24 months, with 20 patients progression-free at 2+-to-36+ (median 16+) months and 10 in first CR at 9+-to-36+ (median 16+) months.

Conclusions: HD-CCV offers a treatment option against topotecan-resistant NB. Results support the concept that combining CPT-11 with very high doses of alkylators can yield greater antitumour effect.

1. Introduction

Standard chemotherapy for high-risk neuroblastoma (NB) includes intensive, myeloablative and salvage regimens using alkylators, platinum compounds, topoisomerase II inhibitors and, most recently, the topoisomerase I inhibitor topotecan.[1–4] For patients who still had NB assessable for response after receiving that wide range of agents, we devised

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a 5-d regimen combining another topoisomerase I inhibitor, irinotecan (CPT-11), with high-dose cyclophosphamide and vincristine (HD-CCV). The underlying rationale included encouraging experience as regards toxicity and anti-NB activity (including against topotecan-resistant NB) in a series of studies at Memorial Sloan-Kettering Cancer Center (MSKCC) using 5-d courses of CPT-11 ± temozolomide (TMZ) or high-dose cyclophosphamide (without vincristine).[5–7] Another consideration was the absence of increased toxicity when vincristine was used with high-dose cyclophosphamide–topotecan.[6,8]

CPT-11 was appealing because of its antitumour activity in preclinical models,[9] including topotecan-resistant xenografts,[10] and in patients at relatively non-myelosuppressive dosing[11,12]; its manageable non-haematologic toxicity (diarrhoea); its activity against brain tumours in preclinical and clinical studies[13]; and evidence that it is less affected by P-glycoprotein multi-drug resistance than topoisomerase II inhibitors such as doxorubicin and etoposide.[14] CPT-11 was administered with cyclophosphamide because the mechanism of action of topoisomerase I inhibitors – mainly S-phase-specific obstruction of DNA replication – supported the combined use with an alkylating agent as a strategy for enhancing antitumour effect. The high dosage of cyclophosphamide was aimed at (1) exploiting the log–linear relationship between alkylator dose and antitumour activity, and (2) preventing development of human anti-mouse antibody (HAMA) if patients were later to receive immunotherapy with the murine anti-G_{D2} 3F8 monoclonal antibody.[15,16] Vincristine was added based on preclinical observations that it has additive[17] or synergistic[18] anti-cancer effects when combined with topoisomerase I inhibitors. We now present a retrospective analysis of results with HD-CCV.

2. Patients and methods

The development of HD-CCV was based on prior MSKCC studies using its individual agents – cyclophosphamide, CPT-11 and vincristine – in identical dosages.[5–8] HD-CCV was preceded and followed by extent-of-disease evaluations plus tests of major organs, including echocardiogram, because the patients were being considered for enrolment on formal protocols. In accordance with hospital rules, informed written consents for treatment were obtained from guardians after they understood the side effects of each agent, the certainty of severe pancytopenia and attendant risks of infection or haemorrhage and the possibility of unforeseen toxicities. The guardians were uniformly well-versed in toxicity issues, given the extensive prior intensive therapy of the patients. An institutional review board waiver was obtained for analysis of patient records.

2.1. Patient characteristics and prior therapy

The subjects of this retrospective study were all 38 unselected MSKCC patients (53% male) who received HD-CCV as treatment for primary refractory NB (Table 1). Thus, when treated with HD-CCV, all patients had NB assessable for response but no history of relapse or progressive disease (PD): 36 had NB in BM, as documented by histology plus MIBG scan ($n = 21$), MIBG scan alone ($n = 9$), or histology alone ($n = 6$), whereas two patients had residual soft tissue NB in the abdomen. All had high-risk stage 4 NB with BM involvement at initial presentation: 34 were diagnosed at age $\geqslant$23 months, and the 4 younger patients had *MYCN*-amplified NB.

Table 1 – Clinical data on 38 patients treated with HD-CCV.

Age at diagnosis (years)	1.3[a]–12.9[b]
Median	4.0
Months from diagnosis	4.5–15.0
Median	7.0
MYCN-amplified	7 (23%) of 30 assayed
Prior therapy	
No. of cycles	6–12, median 7
Topotecan	38 (100%)
Cisplatin	38 (100%)
High-dose CDV	36 (95%)
Stem cell transplant	9 (24%)
Irinotecan[c]	6 (16%)
Temozolomide	5 (13%)
^{131}I-MIBG	5 (13%)
Response to HD-CCV	
Complete	5 (13%)
Partial	3 (8%)
Mixed	5 (13%)
Stable (no regression)	26 (68%)
Progressive disease	0

CDV, cyclophosphamide (4200 mg/m^2)–doxorubicin (75 mg/m^2)–vincristine.

[a] Four patients were $\leqslant$20-months-old, and all had *MYCN*-amplified disease.

[b] Two patients were adolescents, i.e. >10 years old at diagnosis.

[c] Same dosage and schedule as in HD-CCV.

All 38 patients had previously received chemotherapy regimens for high-risk NB, including Children's Oncology Group protocols (A3973,[19] $n = 12$; ANBL0532,[3] $n = 13$); the MSKCC N7 protocol[20] ($n = 6$); the Pediatric Oncology Group protocol 9640 ($n = 4$); the rapid COJEC protocol[21] ($n = 2$); and a single-institutional protocol similar to ANBL0532 ($n = 1$). Eight (21%) patients were on treatment for $\geqslant$12 months before HD-CCV. All 38 patients (100%) had prior exposure to topotecan,[1–3] 9 (24%) were status-post myeloablative therapy with PBSC transplantation, 6 (16%) had received CPT-11,[5–7] and 5 (13%) each had received TMZ[7] or ^{131}I-MIBG (18 mCi/kg) therapy (Table 1). Thirty-three (87%) patients had received one or more salvage therapies before HD-CCV, while 5 patients proceeded directly to HD-CCV as the initial second-line therapy after incomplete responses to topotecan-containing induction.[3]

2.2. Treatment

After confirmation of grade $\leqslant$2 cardiac, hepatic and renal toxicity by the National Cancer Institute Common Toxicity Criteria Versions 3.0 or 4.0, HD-CCV was administered in the outpatient clinic and comprised: cyclophosphamide 70 mg/kg on days 1 and 2 (140 mg/kg [$\sim$4200 mg/m^2]/course), CPT-11 50 mg/m^2 on days 1–5 (250 mg/m^2/course) and vincristine 0.067 mg/kg or 2 mg/m^2 (whichever was lower, maximum dose 2 mg) on day 1. Cyclophosphamide, mesna, CPT-11 and vincristine were infused as previously described.[5–8] Patients

received a second course of HD-CCV if the first showed anti-NB activity but assessable disease remained and if non-haematologic toxicity was grade ⩽2.

Patients with poor bone marrow (BM) reserve, defined as a persistent platelet count <100,000, could be treated with HD-CCV only if peripheral blood stem cells (PBSCs) were available (i.e. had been previously collected). These patients were scheduled to receive PBSCs as outpatients 3 d after completion of the HD-CCV. Subcutaneous injections of granulocyte colony-stimulating factor (5 μg/kg/d) started 1 d after the infusion of the PBSCs, or when the absolute neutrophil count (ANC) reached ⩽500/μl after completion of the HD-CCV in patients not scheduled for PBSC support.

2.3. *Evaluation of response*

Disease status pre- and post-HD-CCV was assessed by computed tomography or magnetic resonance imaging, ^{123}I-metaiodobenzylguanidine (MIBG) scan, urine catecholamine levels and BM histology (aspirates and biopsies from both posterior iliac crests, and aspirates±biopsies from both anterior iliac crests). BM and radiologic studies were read by MSKCC specialists outside the Department of Pediatrics who had no awareness of the treatment or patient status. Pre- and post-HD-CCV BM was also studied by fluorescence *in situ* hybridisation (FISH) and cytogenetics to exclude secondary leukaemia or myelodysplastic syndrome, in accordance with our policy of checking for this complication in patients to be enroled in, and then while being treated on, formal studies.[22]

The International NB Response Criteria (INRC)[23] were used as modified in the ANBL0532 protocol (ClinicalTrials.gov NCT00567567) to incorporate ^{123}I-MIBG findings: complete response (CR), no evidence of NB in soft tissue, bones, or BM and catecholamines normal; very good partial response (VGPR), primary mass reduced by ⩾90%, no evidence of distant disease in soft tissue, bones, or BM, including negative ^{123}I-MIBG scan and catecholamines normal; partial response (PR), >50% decrease in measurable disease, ^{123}I-MIBG scan improved in all lesions and ⩽1 positive BM site; mixed response (MR), >50% decrease of any lesion with <50% decrease in any other, and ^{123}I-MIBG scan improved in some but not all sites; no response (which is the equivalent of 'stable disease' in other staging systems), <50% decrease but <25% increase in any existing lesion; and PD, new lesion or >25% increase in an existing lesion.

2.4. *Statistical analysis*

The probability of progression-free survival (PFS) was estimated by the Kaplan–Meier method,[24] calculating from the first day of HD-CCV.

3. Results

3.1. *Responses*

Objective responses (5 CR, 3 PR and 4 MR) occurred in 12 (43%) of the 28 patients treated with HD-CCV within 9 months of diagnosis, but a response (MR) was seen in only 1 (10%) of 10 patients on therapy for >10 months before receiving HD-CCV. Thus, overall, objective responses occurred in 13 (34%) patients (3 with and 9 without *MYCN*-amplified NB, and 1 with unknown *MYCN* status), and major responses (CR + PR) were seen in 8 (21%) patients (2 with and 5 without *MYCN* amplification, and 1 with unknown *MYCN* status); no patient had PD (Table 1). The 5 CRs involved BM: 3 by histology alone, 1 by MIBG scan alone, and 1 by both histology and MIBG scan. The 3 PRs involved BM by both histology and MIBG scan. The 5 MRs represented disease regressions evident by MIBG scan alone ($n = 1$) or by both BM histology and MIBG scan ($n = 4$).

As regards the 5 patients for whom HD-CCV was the initial second-line therapy after topotecan-containing induction,[3] 1 had CR, 1 had MR and 3 had NR. The 5 patients previously treated with CPT-11/TMZ all had responses to HD-CCV (2 PRs and 3 MRs). Six patients with incomplete responses to HD-CCV were then treated with CPT-11/TMZ[7]: all had NR.

Twenty patients remain progression-free at 2+-to-36+ (median, 16+) months, including 10 in first CR/VGPR at 9+-to-36+ (median, 16+) months post-HD-CCV. Initial treatments after HD-CCV were 3F8 immunotherapy ($n = 23$)[16], targeted radiotherapy using ^{131}I-3F8 ($n = 9$), and chemotherapy with CPT-TMZ.[7] PFS was 64% (SE±8%) at 24 months and 40% (±12%) at 36 months (Fig. 1). The longest times to PD were 34 and 52 months.

3.2. *Toxicity*

A total of 49 courses were administered to the 38 patients. Modest acute toxicity (e.g. grade 1–2 nausea) allowed outpatient treatment. Grade 2 or 3 diarrhoea sometimes developed during, or within 2–3 d after, a course, but was self-limited or managed with routine medication. One patient developed haemolytic-uremic syndrome and acute respiratory distress syndrome (ARDS), which probably were related to infection, although none was documented; these were the sole unex-

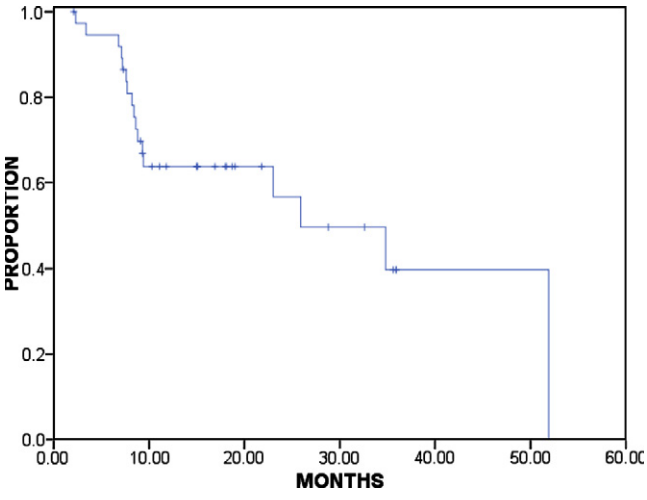

Fig. 1 – Progression-free survival (PFS) of 38 patients with primary refractory neuroblastoma treated by one or two courses of HD-CCV followed by other therapy. PFS is calculated from day 1 of HD-CCV.

pected side effects among the 38 patients. Otherwise, non-haematologic toxicity was grade <2, including no mucositis.

Blood-borne infections were documented in nine (18%) of the 49 courses. Myelosuppression was grade 4. PBSCs (>3 million CD34+ cells/kg) were infused in six patients who had poor BM reserve due to prior myeloablative therapy: their haematologic recovery was uncomplicated, with the ANC rebounding to 500/μl by post-infusion day 7-to-13 (median, 11).

One patient was found by routine surveillance BM studies at 17 months after HD-CCV, which had been followed by 12 cycles of CPT-11/TMZ, to have secondary myelodysplastic syndrome: translocation of the *MLL* (11q23) gene was detected by FISH, and a clonal cytogenetic abnormality – 46, XY, der(19)t(11;19)(q23;p13.1)t(18;19)(p11.2;q13.1) – was identified by karyotype analysis.

4. Discussion

HD-CCV was designed for patients with NB that had responded inadequately to topotecan-containing chemotherapy regimens.[1–4] An important consideration was preclinical evidence that CPT-11 and topotecan are sometimes non-cross-resistant.[10] Topotecan has been extensively used for refractory or relapsed NB[1,2,4] but now is also used in upfront combinations for newly-diagnosed NB[3] – hence, novel salvage chemotherapy regimens are needed. HD-CCV is the first reported regimen combining cyclophosphamide, CPT-11 and vincristine; the high dosing is also noteworthy.

The large experience resulted from our turning to HD-CCV for the many patients referred to our service for treatment of primary refractory NB. The persistence of NB in BM or the primary site, as evidenced by histology or MIBG scan, forebodes a lethal outcome.[25–27] Furthermore, patients who are scanned within days of therapeutic doses of ^{131}I-MIBG are found to have more extensive NB than revealed by standard diagnostic studies.[28] Our strategy is to cytoreduce disease as much as possible using the traditional modalities of chemotherapy, radiotherapy and surgery, and then consolidate CR/VGPR or treat residual BM disease with 3F8[16] and 13-*cis*-retinoic acid (13-cis-RA).[29] The anti-NB activity and modest non-haematologic toxicity of HD-CCV were appealing for inclusion in treatment plans developed for children already exposed to cardio- and nephrotoxic therapy. Another factor in resorting to HD-CCV was the anti-HAMA effect of high-dose cyclophosphamide.[15]

In our large series of patients who still had assessable NB after intensive induction therapy and in 33 (87%) of the 38 patients, after one or more salvage regimens, HD-CCV showed anti-NB activity, with an objective response rate of 34% and a major response (CR + PR) rate of 21%. By strict INRC criteria,[21] 5 of the 13 responses fell into the MR category, usually because of incomplete normalisation of MIBG scans. It may be unrealistic to expect only one or two courses of any chemotherapy to achieve major responses (CR or PR) of widespread disease documented after treatment with the standard active anti-NB agents. This point holds especially for patients on prolonged therapy: indeed, only one response (MR) was noted among the 10 patients in this series who were >10 months from diagnosis, compared to the 43% objective response rate among 28 patients who received HD-CCV within 9 months of diagnosis.

For topotecan-resistant NB, CPT-11/TMZ has emerged as a helpful salvage regimen, with anti-NB activity and modest toxicity.[7,30,31] The far more myelosuppressive HD-CCV achieved responses in all five patients in this series whose NB had proved refractory to CPT-11/TMZ. These findings point to a potential role for HD-CCV in this setting and are consistent with the concept that combining CPT-11 with very high doses of alkylators might yield greater antitumour effect. Of possible relevance in weighing the advantages of one regimen compared to the other, 6 patients with incomplete responses to HD-CCV were then treated with CPT-11/TMZ[7]: all had NR and one developed secondary myelodysplastic syndrome, a well-recognised risk with prolonged exposure to chemotherapy.

Overall, we suggest that HD-CCV provided a clinical benefit in this cohort of patients with an especially poor prognosis: HD-CCV-induced disease reduction likely improved the prospects for prolonged PFS following subsequent treatment with non-chemotherapeutic agents such as 3F8[16] and 13-*cis*-RA.[29] In this regard, as noted in Results, for these 38 patients with refractory disease, PFS dating from treatment with HD-CCV was 59% (SE±10%) at 24 months (Fig. 1), and 10 patients were in first CR/VGPR with a median post-HD-CCV follow-up of 18+ months.

HD-CCV had modest and no unforeseen non-haematologic side effects, with the notable exception of haemolytic-uremic syndrome and ARDS in one patient (attributable to infection). Outpatient treatment was possible using pre-programmed small portable pumps for 24-h infusions of intravenous fluids and mesna. When they occurred, gastrointestinal symptoms were of short duration or responsive to standard medications. Mucositis and other non-haematologic toxicities associated with many chemotherapeutic agents were absent. In short, HD-CCV caused no greater non-haematologic toxicity than the previously described 5-d regimens of CPT-11 plus another alkylating agent (TMZ)[7] or CPT-11 plus high-dose cyclophosphamide administered without vincristine.[6]

As expected, the high dosing in HD-CCV produced grade 4 myelosuppression. Nevertheless, infections were controlled. In patients with thrombocytopenia indicative of depleted BM reserve due to prior ^{131}I-MIBG therapy or myeloablative chemotherapy with stem-cell transplantation, the plan was for HD-CCV to be followed by infusion (in the outpatient clinic) of previously harvested PBSCs. Our experience illustrates the value of collecting abundant PBSCs during induction in NB patients[32]: PBSC support may be needed to allow a full range of salvage therapies if a patient's disease proves resistant to standard treatments.

Prior studies guided the choice of agents, schedule and dosing. CPT-11 has recently been added to the anti-NB armamentarium. As monotherapy, dosages of CPT-11 have been the same or, more often, considerably lower than those in HD-CCV. Various schedules have been explored including CPT-11 alone in 1-to-5 d,[11,12,33] and in fractionated[34] or protracted[35] schedules. In paediatric trials, we and others have used CPT-11 in combination with other agents, including TMZ,[7,30,31] carboplatin[36] and vincristine,[37,38] most often by the 2-week

protracted schedule. Small numbers of patients and differences in prior therapy prevent meaningful comparisons among the different regimens as regards efficacy against NB.

In HD-CCV, the 5-d CPT-11 schedule was retained for two reasons: (1) it suited the 2-d usage of high-dose cyclophosphamide, affording an overlap in timing of maximal myelosuppressive effects; and (2) it minimised the risk of debilitating gastrointestinal toxicity which, in contrast with a protracted schedule,[30] has been distinctly uncommon with 5-d courses, both at MSKCC[5–7] and elsewhere.[11] (Cefixime reduces the gastrointestinal toxicity of the protracted schedule.[35]) The only randomised study to our knowledge directly comparing 5-d versus protracted dosing of CPT-11 involved patients with rhabdomyosarcoma and found no difference in antitumour activity.[38] In a report on successive studies, also in patients with rhabdomyosarcoma, CPT-11 alone proved inferior to CPT-11 plus vincristine as regards to antitumour activity, and no pharmacokinetic interaction between the two agents was found.[37] These results provide valuable clinical validation, beyond the preclinical findings,[17] for adding vincristine to the high-dose cyclophosphamide–irinotecan combination, as in HD-CCV. In conclusion, our experience suggests that HD-CCV should be considered in selected patients with NB. Also, the favourable toxicity profile supports consideration of this regimen for other paediatric solid tumours sensitive to its components.

Conflict of interest statement

None declared.

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