PERGAMON

European Journal of Cancer 36 (2000) 1808–1815

European Journal of Cancer

www.ejconline.com

Induction chemotherapy in metastatic neuroblastoma — does dose influence response? A critical review of published data standards, options and recommendations (SOR) project of the National Federation of French Cancer Centres (FNCLCC)

C.R Pinkerton [a,*], M.P. Blanc Vincent [b], C. Bergeron [c], B. Fervers [c], T. Philip [c]

[a] *Department of Paediatric Oncology, Royal Marsden NHS Trust, Downs Road, Sutton, Surrey SM5 4HW, UK*
[b] *Centre Leon Berard, 28, rue Laennec 69373, Lyon, Cedex 08, France*
[c] *National Federation of French Cancer Centres, rue Tolbac, Paris, France*

Received 11 February 2000; received in revised form 6 June 2000; accepted 23 June 2000

Abstract

The purpose of this study was to determine, from a review of published data, whether in stage 4 neuroblastoma in children over 1 year of age, the dose or scheduling of induction chemotherapy influenced the response rate in distant metastases. Publications relating to induction chemotherapy since the introduction of cisplatin/epipodophyllotoxin combinations were identified using Medline, Current Contents and personal reference lists. Thirteen publications were identified which described 17 regimens involving 948 children. The doses and the scheduling of the various regimens were compared with a standard regimen OPEC (vincristine, cisplatin, teniposide, cyclophosphamide). These were correlated with the reported response rates in the bone marrow. Due to a lack of standardisation in the nature of restaging investigations, timing of restaging and definitions of response it was difficult to compare all studies. The complete response rate at distant metastases ranged from less than 40% to over 90%. For individual drugs; the comparative doses given in each course ranged up to 4.2 g/m^2 for cyclophosphamide, 280 mg/m^2 for cisplatin, 600 mg/m^2 for etoposide and 4.5 mg/m^2 for vincristine. There was no evidence of any positive correlation between response rate in the marrow and either the dose of any individual drug or the schedule used. In contrast to a previous study which included a number of older studies where disease assessment was even more variable, this analysis has failed to show any justification for the routine use of very intensive induction regimens in this disease. Such an approach should only be taken in the context of randomised trials in which timing and methods of reassessment can be standardised. Until such studies demonstrate superiority either in terms of response rate or progression-free survival lower morbidity regimens should remain the standard therapy.

Keywords: Chemotherapy; Neuroblastoma; Dose intensity; Response; Bone marrow

1. Introduction

Approximately 60% of children with neuroblastoma have disseminated disease at presentation. This usually involves bone and bone marrow (INSS stage 4 disease). The outcome in children over 1 year old is worse than in infants (<20% compared with approximately 60% event-free survival (EFS) at 5 years).

Over the past 10–15 years there has been a steady improvement in outcome for poor risk patients, rising from approximately 5 to approximately 20% durable remission. It is unclear to what extent this is due to improved chemotherapy, high-dose therapy with stem cell rescue or *cis*-retinoic acid treatment.

The introduction of cisplatin and epipodophyllotoxin-based regimens in the 1980s for the treatment of advanced neuroblastoma improved response rates and outcome [1]. One of the first regimens to include these agents, OPEC, combined standard doses of cyclophosphamide, vincristine, with cisplatin and teniposide [2]. Complete response rates in the bone marrow exceeded 80% and led to durable remission in a number of patients. At the same time a non-crossresistant regimen cisplatin and teniposide (PE) vincristine, cyclophosphamide, doxorubicin (CADO) was developed by the French Lyon-Marseille-Curie East of France (LMCE)

* Corresponding author. Tel.: +44-181-661-3498; fax: +44-181-770-7168.
E-mail address: rossp@icr.ac.uk (C.R. Pinkerton).

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00189-1

group [3]. This group was also the first to use a high-dose cisplatin-based protocol [4] which was subsequently evaluated by the European Neuroblastoma Study Group (ENSG) [5]. Since then a range of variations on these themes have been used, both in single centre and large national studies.

An analysis published in 1991 demonstrated a striking correlation between dose intensity and both response and progression-free survival, particularly for cisplatin and teniposide [6]. This work has been influential in subsequent strategies where it has been assumed that more would necessarily be better as has been suggested in other cancers [7]. The inevitable and often severe early and late morbidity of this approach has been accepted as unavoidable if advances are to be made into the cure rates of this condition.

As the majority of chemotherapy is given outside formal randomised studies it is important to have a logical basis for defining any 'standard' therapy. In 1996 the National Federation of Cancer Centres (FNCLCC) developed a series of clinical practice guidelines — 'SOR' (Standards, Options and Recommendations) for the investigation, management and follow-up of a range of childhood cancers including neuroblastoma [8]. The present report is based on the methodology used in the SOR analyses, and outlines the methodology and results in the different studies and reassesses the possible effect of dose intensity in light of the recent studies.

2. Patients and methods

The SOR project was initiated in 1993 and is a collaborative venture involving the FNCLCC, 20 French Cancer Centres and specialists from universities, general hospitals and private clinics. There is also an important contribution from the French Society for Paediatric Oncology (SFOP). The main objective is the development of clinical practice guidelines to improve the quality of care and outcome for cancer patients.

The quality of published data must be defined [9–11]. For the SOR guideline development the level of evidence supporting each recommendation is specified using the following classification:

Level A: There exists a well performed meta-analysis or several high quality randomised clinical trials the results of which are clear and homogeneous.

Level B1: There exist clinical trials, single-arm studies or historical comparisons which when taken together indicate a certain conclusion.

Level B2: There exist prospective or retrospective studies which when taken together indicate a certain conclusion.

Level C: There exist randomised trials, single-arm studies or historical comparisons which when taken together are heterogeneous and fail to produce any clear conclusion.

Level D: There are no relevant published data or only a series of case reports.

Expert agreement: Despite the absence of relevant published data the view of the experts is unanimous. Such expert opinion must be validated by internal and external review.

A *Standard* intervention is one for which the results are known and which are considered of benefit, inappropriate or harmful by unanimous consent. They are equivalent to absolute indications or contraindications.

2.1. Literature review and data collection

Relevant data were identified from the published literature using Current Contents and Medline between 1984 and 1999. Personal reference lists were utilised and in some circumstances investigators were directly contacted to obtain further information or updates. The reference list bibliography of primary articles was also searched.

For the purpose of this critical analysis it was decided to review in detail studies published since the introduction of chemotherapy regimens that included cisplatin and epipodophyllotoxins. Studies which failed to provide adequate information on the methods of response assessment, the definitions of response or the response details at individual sites were excluded as no meaningful interpretation of dose intensity in relation to response rate was possible.

The criteria for inclusion in this review were:

(1) Studies relating to the treatment of metastatic neuroblastoma in children over the age of 1 year at diagnosis;
(2) Adequate details of the chemotherapy used with regard to drug doses and scheduling;
(3) Details of response either at individual sites of disease or overall response rates;
(4) Details of treatment-related morbidity and mortality.

Some studies contained both Stages 3 and 4 and unless response data were presented separately these were not included.

The planned end points of the analysis were:

(1) The initial response rate to chemotherapy;
(2) Treatment-related morbidity and mortality.

The initial response rates were contrasted taking into account the type of chemotherapy given, the number of drugs used and the doses used compared with the standard cyclophosphamide, vincistine, cisplatin, teniposide (OPEC) regimen.

Responses assessed by bone marrow morphology/cytology and on metaiodobenzylguanidine (MIBG) scanning were used, but only a small number of studies documented MIBG response specifically. Because of the variation in the methods of assessing and documenting response at the primary site or at other metastatic sites these were not analysed. Table 1 summarises the various restaging systems used.

For this review, complete marrow response includes all those defined in the text to have had a complete response (CR) or very good partial response (VGPR) or good partial response (GPR) (for detailed definitions see later) where individual site response was not specified. OPEC was selected as the comparator regimen because it contains conventional doses of four of the most active agents used in neuroblastoma.

The initial response to induction chemotherapy and not the final response or ultimate progression-free survival or overall survival was considered. Due to the wide variation in the types of consolidation therapies used after initial chemotherapy no attempt was made to correlate ultimate outcome with initial treatment given. Subsequent treatment involved continuing the same regimen, giving high-dose myeloablative regimens, immune modulators, differentiating agents and radiolabelled MIBG therapy. In some studies only patients in CR/VGPR proceeded to myeloablative regimens, in others this applied to those in PR.

3. Results

Thirteen relevant publications were identified which described 17 regimens [2,3,5,13–22]. Only one was a randomised study [20]. The drugs used, the various combinations given and the doses of each drug are outlined in Tables 2 and 3. The methods of response assessment and the systems of definitions used are listed in Tables 1 and 4. In addition to variations in the method of obtaining bone marrow, the analysis also varied. Some studies used cytology alone, others a range of immunohistochemical markers. Often the precise methods were not described in detail. The complete response rates in bone marrow are listed in Table 5.

The response rates (CR/VGPR/GPR) varied widely ranging from 27% in the POG 81a study arm, with doxorubicin and low-dose cyclophosphamide to 96% in the N6 regimen, combining high-dose cyclophosphamide/doxorubicin with high-dose cisplatin/etoposide. The low

Table 1
Response assessment systems

MSK (post surgical evaluation N4 to N6)	
CR	Resolution of distant metastases including normalisation of bone scans, bone marrow (on multiple examinations) and serum and urine biochemical profile; complete resection of tumour masses with no viable cells identified on histological examination.
GPR	As with CR but histopathological evidence of viable malignant cells in the tumour grossly resected at second-look surgery or CR on imaging.
PR	Absence of tumour-related symptoms, more than 50% decrease in tumour size and in all other disease markers and no new metastases.
AIEOP	
CR	Disappearance of all evidence of disease which includes return to normal levels of VMA and HVA urinary excretion and at least improvement of any osteolytic lesion.
PR	Greater than 50% decrease in all measurable tumour lesions, no more than minimal bone marrow infiltration as defined by sporadic tumour cell aggregates on smears, improved bone lesions by X-ray and/or bone scan.
POG	
CRC	>90% regression of the primary tumour with complete regression of all metastatic disease including healing of bone lesions.
CRS	Above plus removal of primary at delayed surgery.
PRC	50–90% regression of the primary tumour and >50% regression of metastatic disease at all involved sites, with evidence of bone healing.
INRC	
CR	Complete disappearance of all primary and metastatic disease and the normalisation of catecholamines and metabolites.
VGPR	90–99% volume reduction in the primary tumour with clearing of all measurable metastatic disease and normalisation of catecholamines. Residual abnormalities on technetium bone scan that are attributable to incomplete bone healing are allowed; MIBG scan (if performed) must be negative at all metastatic sites.
PR	Greater than 50% volume reduction in the primary tumour and all metastatic sites. One residual positive bone marrow site is permitted if this reflects a decrease from the number of sites positive at the time of diagnosis, e.g. two to four sites positive at diagnosis.

CR, complete response; PR, partial response; GPR, good partial response; CRC, complete response clinical; PRC, partial response clinical; VGPR, very good partial response; AIEOP, Associazione Italiana di Ematologica e Oncologia Pediatrica; POG, Pediatric Oncology Group; INRC, International Neuroblastoma Response Criteria; MSK, Memorial Sloan Kettering; VMA, vanillylmandelic acid; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; CRS, complete response surgical.

Table 2
Outline of chemotherapy regimens

Study [Ref.]	Chemotherapy regimen	Total number of courses	Schedule	Year of study
N4SE [13]	DOX, CP, 5-FU, VCR, AraC, Hydroxyurea	3–5	Sequential	80–87
N5 [14]	DOX, CP, VCR (CAV)/CDDP, ETOP (PVP)	7	Sequential	NS
N6 [15]	DOX, CP, VCR (CAV)/CDDP, ETOP (PVP)	6	Alternating	NS
CCG321P [16]	CP, CDDP, TENIP, DOX	3–7	Sequential	86–94
OPEC (D) [2]	VCR, CDDP, TENIP, CP (DOX)	6–12	Sequential	79–81
PECADO [3]	CDDP, TENIP, (PE)/CP, DOX, VCR (CADO)	6	Alternating	83–85
ENSG3 [5]	IFOS, VCR, DOX (IVAD)/CDDP, ETOP (HIPE)	4	Alternating	86–87
AIEOP NB 82 [17]	PEPTICHI/CDDP, TENIP	4	Sequential	82–84
AIEOP NB 85 [17]	PEPTICHI/CP, VCR, CDDP/DOX, TENIP	4	Sequential	85–89
Rapid OPEC [18]	CDDP, ETOP, VCR/CDDP, VCR/ETOP, VCR, CP/CDDP, VCR	4	Sequential	NS
SFOP NB 87 [19]	CP, DOX, VCR (CADO)/CDDP, ETOP (CVP)	4	Alternating	90–92
POG 81 [20]	Randomised DOX, CP versus CDDP, TENIP	5	Sequential	81–84
DCECaT [21]	Desferoxamine, CP, ETOP, TP, CARBO	4	Sequential	92–93
SNSG [22]	CP, DOX/CDDP, TENIP	6	Alternating	87–92

DOX, doxorubicin; CP, cyclophosphamide; VCR, vincristine; CDDP, cisplatin; tenip, teniposide; ETOP, etoposide; 5-FU, fluorouracil; PEPTICHI, peptichimio; IFOS, ifosfamide; AraC, cytosine arabinoside; TP, thiotepa; CARBO, carboplatin; NS, not specified. See Table 4 for study abbreviations. With the exception of Rapid OPEC (every 10 days) and the SNSG regimen (every 4 weeks) chemotherapy was scheduled to be repeated every 3 weeks. With some regimens treatment was given at count recovery a few days earlier or later.

Table 3
Doses of chemotherapy (mg/m^2) per course or 21 days.

Study	Drug					
	DOX	CP	TENIP	ETOP	CDDP	VCR
OPEC		600	150	–	100	1.5
OPECD	40	600	150	–	100	1.5
N4Sea	30	2000[a]	–	–	–	3
N4Seb	30	4000[a]	–	–	–	3
N5	45	4200	–	450	120	3
N6	75	4200	–	600	200	4.5
CCG321P	30	1800	100	–	60	–
PECADO	60	1500	160	–	100	3
ENSG3	60	3000[b]	–	500	200	1.5
AIEOP NB 85	45	600	125	–	200	1.5
AIEOP NB 82	–	–	100	–	90	–
Rapid OPEC	–	1000	–	500	280	4
SFOP NB 87	60	1500	–	500	200	3
POG 81a	35	1050	–	–	–	–
POG 81b	–	–	100	–	90	–
DCECaT	–	600	–	300	1000 carboplatin	–
SNSG	45	1050	180	–	200	–

For abbreviations see Table 2.
[a] Average of escalating dose.
[b] This is an equivalent dose of CP for IFOS.

response rates in the former studies to some extent reflect the different definition of CR, being postsurgical and requiring complete resection. When this stricter definition of CR is applied as opposed to VGPR, the rates are uniformly lower. Information from technetium bone scans are unreliable at this early stage and do not distinguish between healing lesions that take up isotope and residual active disease. Too few studies included reassessment with MIBG to use this technique in any comparison.

3.1. Doses used in various regimens

Table 2 lists the doses of the individual drugs given with each course of chemotherapy. As can be seen from the table, over this period of induction chemotherapy there was a wide range in doses, particularly for certain drugs. The greatest range was with cyclophosphamide, which ranged from 0.6 g/m^2 in the Italian Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) NB 85 study among others, to approximately 4 g/m^2 per

Table 4
Method of response assessment

Study	System	Bone	MIBG
N4SE	MSK	Tc	−
N5	INRC	Tc	+/−
N6	INRC	Tc	+
CCG321P	INRC	Tc	−
OPEC/D	ENSG	Tc	−
PECADO	ENSG	Tc	−
ENSG3	INRC	Tc	+
AIEOP NB 82,83	AIEOP	Tc	−
Rapid OPEC	INRC	Tc	−
SFOP NB 87	INRC	MIBG only	+
POG 81	POG	Tc	−
DCECaT	INRC	Tc	+
SNSG	ENSG	Tc	+

MIBG, metaiodobenzylguanidine; ENSG, European Neuroblastoma Study Group; INRC, International Neuroblastoma Response Criteria; MSK, Memorial Sloan Kettering; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; POG, Pediatric Oncology Group; OPEC, vincristine, cisplatin, teniposide, cyclophosphamide; SNSG, Spanish Neuroblastoma Study Group; Tc, technetium.

course in the Memorial Sloan Kettering (MSK) N-4-6 regimens. For doxorubicin the doses varied from 30 to 75 mg/m^2. Although some regimens contained high doses of doxorubicin, because these generally were alternating regimens, e.g. European Neuroblastoma Study Group (ENSG3), the overall dose intensity of the drug was low. With the exception of the rapid OPEC regimen in which a total of 800 mg/m^2 was given in divided courses, the dose of etoposide varied little between protocols. In most regimens containing high-dose cisplatin (CDDP), the drug was given in alternate courses and combined with only etoposide, as a result the dose intensity of 'high-dose' CDDP was unremarkable. The exception was rapid OPEC in which CDDP was given at the nadir on days 10 and 30 which significantly increased the overall dose intensity. The dose of vincristine (VCR) varied widely from 1.5 to 4.5 mg/m^2.

The least dose-intensive regimen was that used in the two-drug Paediatric Oncology Group (POG) study, and the highest the N4SE regimen, where very high-dose cyclophosphamide was given with each course. The two other regimens that stand out as having high-dose intensity compared with standard OPEC, are the N6 and rapid OPEC regimens.

3.2. Correlation between dose and response

Table 5 lists the complete marrow response rates to induction chemotherapy in the 17 protocols along with the number of patients in each study, the time of reassessment and the method of marrow assessment used. Even allowing for the small numbers of patients in some studies, it appears that the highest CR rates were seen in the following studies: N4SEb, N5, N6, OPEC, OPECD, PECADO, AIEOP NB85 and rapid OPEC.

There is no clear relationship between the achievement of marrow CR and either the dose of any individual drug, or the schedule of the regimen. In the three studies where MIBG response was documented, CR ranged from 44 to 83% (4/9 ENSG3, 69/151 SFOP NB87), 20/24 N6). In the DCECaT study the MIBG response was not clearly stated or deducible from the data. Moreover upon review, the MIBG data from the SNSG study were also unclear. No conclusions can be

Table 5
Complete responses in bone marrow in relation to time of evaluation after start of treatment and method of assessment

Study	Number of evaluable patients[a]	Complete response *n* (%)	Time (months)	Method[b]
N4SEa	14	4 (29)	5	'Multiple'
N4SEb	33	23 (70)	5	'Multiple'
N5	14	13 (90)	5	4+2
N6	24	23 (96)	5	4+2
CCG321P	157	89 (57)	8	'Multiple'
OPEC	13	13 (100)	7–9	2+2
OPECD	10	8 (80)	7–9	2+2
PECADO	35	26 (74)	5	4+6
ENSG3	36	17 (47)	3	2+2
AIEOP NB85	106	81 (76)	3	At least 1 aspirate
AIEOP NB82	75	43 (57)	3	At least 1 aspirate
Rapid OPEC	9	7 (78)	3	2+2
SFOP NB 87	164	108 (66)	3	2+2
POG 81a	70	19 (27)	4	At least 1 aspirate
POG 81b	64	22 (34)	4	At least 1 aspirate
SNSG	58	27 (47)	4	Aspirate ? number
DCECaT	43	22 (50)	3	4 Trephines

[a] Fewer patients were available for response than survival in some studies for various reasons.
[b] 2+2, 2 aspirates+2 trephines; 4+2, 4 aspirates+2 trephines; 4+6, 4 aspirates+6 trephines.

drawn regarding MIBG response and the nature of chemotherapy.

The overall induction strategies are outlined in Table 6. It appears that the regimens based on high-dose CDDP had high CR rates, but comparable rates were also documented in some regimens that lacked cisplatin (N45Eb) or contained standard doses (OPEC, PECADO).

It proved impossible to draw any firm conclusions regarding the relative toxicities of the different regimens from the published data. Two studies did not specify whether there were any treatment-related deaths. Eight reported no toxic deaths and the median death rate in the other studies was 8% (range: 0–23). The death rates in the most intensive regimens were not higher i.e. 0/38 for N5/N6, 5/192 for SFOP NB87, 0/51 for ENSG3.

Seven studies gave little or no details of haematological or other toxicity. Seven gave details of toxicity but due to a lack of standardisation they were difficult to compare. In some, the overall incidence of low blood counts was presented. In others only the percentage of patients with low counts or the duration of myelosuppression was described. Only one described duration of hospitalisation for complications. Too few studies systematically assessed either renal function or hearing for these to be compared.

It would have been of interest to determine to what extent the initial response correlated with outcome. Unfortunately, not only did subsequent consolidation treatment vary widely but the small number of patients in most studies precluded any useful comparison between regimens with regard to eventual outcome.

Table 6
Treatment strategies in relation to marrow complete response (CR) (%)

	Study	CR (%)
High-dose CDDP	Rapid OPEC	78
	N6	96
	SFOP NB87	66
	AIEOP NB85	76
	SNSG	47
	ENSG3	47
High-dose CP	N4SEa	29
	N4SEb	70
	N5	90
Standard dose	AIEOP NB82	57
	PECADO	74
	OPEC±(D)	91
	CCG321P	57
	POG 81	40
	DCECaT	50

See Table 4 for study abbreviations.

4. Discussion

The aim of the FNCLCC SOR project is to provide evidence-based guidelines for implementation at local, regional or national level. In the case of induction chemotherapy for neuroblastoma there is no level A evidence. The only published randomised study showed no significant difference in postsurgical CR rate between regimens containing cyclophosphamide and doxorubicin or cisplatin/teniposide.

Three modifications in chemotherapy strategy have been introduced over the past 15 years. These are:

(1) Use of alternating 'non-cross resistant' regimens;
(2) Dose increases of cisplatin, vincristine and cyclophosphamide/ifosfamide; and
(3) Rapid, dose-intense, scheduling.

Any attempt to compare data from different studies is fraught with problems due to differences in definitions of stage and response, heterogeneity of studies and results, the available data leading to level C evidence. In neuroblastoma, the situation is more complex than other paediatric tumours because of the range of techniques used to reassess disease status.

The definition of stage 4 disease has, unlike other stages of disease in neuroblastoma, been altered little over the years. It is defined as any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs except as defined for stage 4S. Stage 4S is defined as localised primary tumour with dissemination limited to skin, liver and/or bone marrow, limited to infants less than 1 year of age. This analysis was confined to children over 1 year of age.

There are two main factors that might change the percentage of patients defined as having distant metastatic disease. These are the use of more extensive bone marrow investigation and MIBG scanning at diagnosis. It is inevitable that performing several site aspirates or trephines will lead to the detection of patchy infiltrates of tumour not detected by one or two aspirates. In fact, the majority of children with stage 4 disease have extensive marrow involvement at presentation which does not require an exhaustive search to detect it. There remains some controversy about the ability of MIBG scanning to detect marrow or bone disease that is not found on haematological investigation or technetium bone scan. Some investigators claim that MIBG is the most sensitive method to detect either cortical bone or marrow disease, whereas others have shown that the various tests are complementary, none being absolutely reliable. In the reassessment of disease it is likely that the older, less stringent, methods will overestimate the CR rate by failing to detect minor residual disease. This must be borne in mind when comparing different series and makes interpretation of the early phase II and phase III data difficult.

Definitions for response assessment have been provided by the INSS working group [12]. Six groups applied these definitions — Memorial Sloan Kettering, the Children's Cancer Group (CCG), ENSG, Societé Française D'Oncologie Pediatrique (SFOP) and the Spanish Neuroblastoma Study Group (SNSG). Two applied the ENSG criteria which preceded the INSS [2]. The other studies applied national or local definitions. In all but one of the studies, technetium was the standard test for cortical bone disease. In the most recent SFOP studies this test has only been performed in the event of MIBG negativity. In five studies MIBG was used in the reassessment of disease but the results were reported in detail in only three of these. The '2 + 2' marrow/trephine assessment as recommended by the INSS group was applied in four studies. In three only one or more aspirates were required, whereas at the other extreme the French studies, e.g. PECADO have used multiple aspirates and 4-trephines. A lack of standardisation still exists even in groups who are applying the INSS criteria with some only performing '2 + 2' and others continuing to do more extensive studies including immunological assessment.

The definition of response at the primary site is even more variable. In some studies, the response was only defined after surgery to the primary tumour and CR required complete resection. In others a reassessment was done prior to surgery with definition of response at distant sites being distinguished from that at the primary.

Taking into account all these reservations the data in this review suggest that there is no advantage to the use of alternating schedules, compared with the original 3-weekly four- or five-drug combinations.

With regard to dose, it is of note that the results of the N4SEa study with 2 g/m^2 of cyclophosphamide were poor and a doubling of the dose as in the N4SEb study, more than doubled the response rate. The use of 9 g/m^2 ifosfamide in the ENSG3 regimen was, however, not associated with improved results. The impressive response rates with N5 and N6 must be reproduced elsewhere with larger numbers as is underway in the current SFOP/UKCCSG stage 4 pilot study.

With cisplatin the evidence of a dose effect is also suggested, but there are regimens with impressive response rates without such high doses. The latter will invariably have an adverse effect on renal and auditory function, although these are often poorly documented.

The wide ranging number of drugs used, doses given and schedules adopted makes formal mathematical calculation and comparison of relative dose intensity difficult and of limited value.

The clear dose-response and dose outcome relationship demonstrated by Cheung may apply to early studies in which the doses given were low or where only two or three drugs were used. Regimens with grossly suboptimal dose intensity will have poor response and outcome but it can not be concluded that any relationship is linear above a certain dose. Such an assumption has led to the widespread use of intensive high morbidity regimens in single arm studies. It is unfortunate that over this period only one large randomised study has been performed to address the specific issue of dose intensity. This is the recently completed ENSG 5 study which compares standard dose OPEC/OJEC (the latter substitutes carboplatin for cisplatin in alternate courses) with the rapid COJEC regimen. The dose intensity of all drugs is doubled by applying both individual dose increases and the strategy of chemotherapy administration every 10 days as in the rapid OPEC pilot study.

It proved difficult to compare the relative morbidity of the different regimens. Inevitably, the death rate was highest in the earliest studies (OPEC and OPECD) reflecting the supportive care experience and facilities at that time. With appropriate care this rate should be less than 3%. The more relevant comparison is non-fatal morbidity related to the degree and duration of myelosuppression, i.e. infections and platelet requirements, renal and auditory toxicity related to cisplatin and other grade 3/4 toxicities. Moreover, the duration spent in hospital is a useful reflection of both the complexity of chemotherapy and the morbidity and has major financial implications.

To some extent, it is logical to assume that the more intensive regimens will be associated with more significant toxicity but it is important that the nature of these toxicities is clearly documented. This information was available for the N6, ENSG3, rapid OPEC and SFOPNB87 regimens although they cannot be directly compared with each other.

It is acknowledged that potential differences in response rates may have been missed due to the variations in methods and timing of evaluations. However, on the basis of the published data, the conclusions of the SOR group are simply that induction chemotherapy should contain cyclophosphamide, platins, doxorubicin and etoposide or teniposide, i.e. no specific regimen can be selected as standard. It was not felt that there were comparative data sufficient to reach level B evidence and it was recommended that all patients be included on formal national studies.

At the present time, the candidate intensive regimens that could be compared with any of the conventional dose protocols are high-dose cisplatin/etoposide such as the SFOP NB87 protocol and the MSK N6 regimen. These studies would need to be carried out at an international level in order to rapidly recruit sufficient patients to answer these important questions within a reasonable time. If there are deemed to be questions of higher priority such as high-dose therapy or immunotherapy, on the basis of current evidence, these should be built around standard dose induction regimens.

References

1. Hayes FA, Green AA, Casper J, *et al*. Clinical evaluation of sequentially scheduled cisplatin and VM26 in neuroblastoma. *Cancer* 1981, **48**, 2310–2317.
2. Shafford EA, Rogers DW, Pritchard J. Advanced neuroblastoma: improved response rate using a multiagent regimen (OPEC) including sequential cisplatin and VM26. *J Clin Oncol* 1984, **2**, 742–747.
3. Bernard JL, Philip T, Zucker JM, *et al*. Sequential cisplatin/VM26 and vincristine/cyclophosphamide/doxorubicin in metastatic neuroblastoma: an effective alternating non cross resistant regimen? *J Clin Oncol* 1987, **5**, 1952–1959.
4. Hartmann O, Pinkerton CR, Philip T, *et al*. Very high dose cisplatin and etoposide in children with untreated advanced neuroblastoma. *J Clin Oncol* 1988, **6**, 44–50.
5. Pinkerton CR, Zucker JM, Hartmann O, *et al*. Short duration, high dose, alternating chemotherapy in metastatic neuroblastoma (ENSG 3C induction regimen). *Br J Cancer* 1990, **62**, 319–323.
6. Cheung NK, Heller G. Chemotherapy dose intensity correlates strongly with response, median survival and median progression free survival in metastatic neuroblastoma. *J Clin Oncol* 1991, **9**, 1050–1058.
7. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian cancer. *J Clin Oncol* 1987, **5**, 756–767.
8. Fervers B, Bonichon F, Demard F, *et al*. Methodologie de developpement des standards, options et recommandations et therapeutiques en cancerologie. *Bulletin du Cancer* 1995, **82**, 754–760.
9. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non small cell lung cancer. *J Clin Oncol* 1997, **15**, 2996–3018.
10. Canadian Medical Association. The Canadian task force on the periodic health examination. *J Clin Oncol* 1997, **15**, 2996–3018.
11. Sackett DL. Rules of evidence and clinical recommendation on the use of anthrithrombotic agents. *J Clin Oncol* 1997, **15**, 2996–3018.
12. Brodeur GM, Pritchard J, Berthold F, *et al*. Revisions of the International Criteria for neuroblastoma diagnosis, staging and response to treatment. *J Clin Oncol* 1993, **11**, 1466–1477.
13. Kushner BH, Helson L. Co-ordinated use of sequentially escalated cyclophosphamide and cell cycle specific chemotherapy (N4SE protocol) for advanced neuroblastoma: experience with 100 patients. *J Clin Oncol* 1987, **5**, 1746–1751.
14. Kuschner BH, O'Reilly RJ, LaQauglia M, *et al*. Dose intensive use of cyclophosphamide in ablation of neuroblastoma. *Cancer* 1990, **66**, 1095–1100.
15. Kuschner BH, LaQuaglia MP, Bonilla MA, *et al*. Highly effective induction therapy for stage 4 neuroblastoma in children over 1 year of age. *J Clin Oncol* 1994, **12**, 2607–2613.
16. Stram DO, Mattay KK, O'Leary M, *et al*. Consolidation chemotherapy and autologous bone marrow transplantation versus continued chemotherapy for metastatic neuroblastoma: a report of two concurrent Children's Cancer Study Group studies. *J Clin Oncol* 1996, **14**, 2417–2426.
17. DeBernardi B, Carli M, Casale F, *et al*. Standard dose and high dose peptichimio and cisplatin in children with disseminated poor risk neuroblastoma: two studies by the Italian Co-operative Group for Neuroblastoma. *J Clin Oncol* 1992, **10**, 1870–1878.
18. Pearson AJD, Craft AW, Pinkerton CR, *et al*. High dose rapid schedule chemotherapy for disseminated neuroblastoma. *Eur J Cancer* 1992, **28A**, 1654–1659.
19. Coze C, Hartmann O, Frappaz D, *et al*. NB87 induction protocol for stage 4 neuroblastoma in children over 1 year of age: a report from the French Society of Pediatric Oncology. *J Clin Oncol* 1997, **15**, 3433–3440.
20. McWilliams NB, Hayes FA, Green AA, *et al*. Cyclophosphamide/doxorubicin vs cisplatin/teniposide in the treatment of children older than 12 months of age with disseminated neuroblastoma: a Pediatric Oncology Group randomised phase 2 study. *Med Ped Oncol* 1995, **24**, 176–180.
21. Donfrancesco A, DeBernardi B, Carli M, *et al*. Deferoxamine followed by cyclophosphamide, etoposide, carboplatin, thiotepa induction regimen in advanced neuroblastoma/preliminary results. *Eur J Cancer* 1995, **31A**, 612–615.
22. Castel V, Garcia-Miguel P, Melero C, *et al*. The treatment of advanced neuroblastoma. Results of the Spanish Neuroblastoma Study Group (SNSG) studies. *Eur J Cancer* 1995, **31A**, 642–645.