Citation

Niemeijer, N. D. (2017, March 29). *Paragangliomas: Clinical Picture*. Retrieved from https://hdl.handle.net/1887/47852

Cover Page

Universiteit Leiden

Chapter 7

Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis

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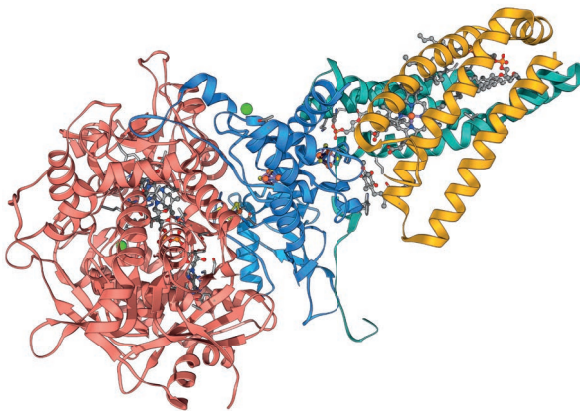
Abstract

Background: Chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD) can be used for palliative treatment of malignant pheochromocytoma and paraganglioma. However, the precise effect of this chemotherapeutic regimen on tumor volume is unclear. The main objective of this study was to perform a systematic review and meta-analysis assessing the effect of chemotherapy with CVD on tumor volume in patients with malignant paraganglioma/pheochromocytoma.

Methods: A literature search was performed in October 2013 to identify potentially relevant studies. Main outcomes were the pooled percentages of complete response, partial response and stable disease after chemotherapy with CVD. A meta-analysis was performed with an exact likelihood approach using a logistic regression. Pooled percentages with 95% confidence intervals (CI) were reported.

Results: Four studies concerning a total of 50 patients with malignant paraganglioma/pheochromocytoma reported on treatment with a combination of CVD chemotherapy. A meta-analysis of the effect of chemotherapy on tumor volume showed pooled percentages of complete response, partial response and stable disease of, respectively, 4% (95% CI: 1%-15%), 37%(95% CI: 25%-51%) and 14% (95% CI: 7%-27%). Only two studies concerning a total of 35 patients assessed the response on catecholamine excess; pooled percentages for complete, partial and stable hormonal response were 14% (95% CI: 6%-30%), 40% (95% CI: 25%-57%) and 20% (95% CI: 10%-36%), respectively. Duration of response was also reported in only two studies with a median duration of response of 20 months and 40 months.

Conclusions: Data on the effects of a combination of CVD chemotherapy on malignant paraganglioma/pheochromocytoma suggest that a partial response concerning tumor volume can be achieved in about 37% of patients and a partial response on catecholamine excess in about 40% of patients. However, in the included studies, the protocol when to initiate treatment was not well described. Therefore, it can not be excluded that the reported effect of chemotherapy on tumor volume reflects the natural course of the disease, at least partially.

Introduction

Background

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors (NETs) of paraganglia. They derive from either sympathetic chromaffin tissue in adrenal and extraadrenal locations (sympathetic PGL or sPGL) or from parasympathetic tissue of the head and neck (HNPGL).[1] Approximately 80% of PGLs arise from the adrenal medulla and are referred to as pheochromocytoma (PCC).[1,2] Although the majority of PGLs are benign, there is a risk of malignant degeneration of 10% for PCC and 10-20% for sPGL.[3] Malignant disease is defined as the presence of metastatic lesions at sites where neuroendocrine tissue is normally absent.[4-7] The prognosis in malignant PGL/PCC is known to be poor and treatment remains basically palliative. The overall 5-year survival in patients with malignant PGL/PCC is less than 50%.[3,8,9] Patients with metastatic tumors also have high morbidity rates from excessive catecholamine secretion, hypertension and cardiovascular complications. Systemic treatment options include radionuclide therapy with ^{131}I-MIBG[10] or radiolabelled somatostatin analogues.[11] A recent meta-analysis on the effects of ^{131}I-MIBG therapy on malignant PGL/PCC suggests that stable disease concerning tumor volume and a partial hormonal response can be achieved in over 50% and 40% of patients respectively.[12]

Combination chemotherapy of cyclophosphamide, vincristine and dacarbazine (CVD) for the treatment of malignant PGL/PCC was introduced in 1985 by Keiser *et al.* [13] Three years later, Averbuch *et al.* presented a study in which 14 patients with malignant PGL/PCC were treated with this combination regimen of CVD. They reported a tumor response rate (complete and partial) of 57%.[14] Combination chemotherapy with CVD produced responses of 80% in children with advanced neuroblastoma, neuroendocrine tumors with similar clinical and biologic characteristics as PCC.[15]

At present, the precise effect of CVD chemotherapy for the treatment of malignant PGL/PCC is unclear. In 2007, Scholz *et al.* published a review on the current treatment of malignant PCC, including CVD chemotherapy.[16] They concluded that the CVD scheme seems to be effective at modest toxicity in a significant proportion of patients; however, remissions are rather short and are often followed by complete therapeutic failure after relapse.[16] A meta-analysis assessing this effect has never been performed.

Objective of the study

The aim of the present study was to perform a systematic review and meta-analysis of the effects of CVD chemotherapy on tumor volume in malignant PGL/PCC. Secondary objectives were to assess biochemical response (i.e. hormonal overproduction), overall survival, progression-free survival and toxicity.

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Materials and methods

Eligibility criteria

Studies assessing the effect of the combination of chemotherapy with CVD on tumor volume of malignant PGL/PCC were eligible for inclusion. Malignant PGL/PCC was defined as the presence of metastases in non-neuroendocrine tissue distant to the primary tumor.[4-7] Studies concerning patients with non-malignant PGL/PCC according to this definition were excluded, e.g. locally invasive PGL/PCC without metastases, unless data for patients with metastatic PGL/PCC could be extracted separately.

The analysis aimed to assess the percentage of PGL/PCC-patients with tumor response after chemotherapy, with biochemical response (i.e. levels of catecholamines and/or their metabolites), overall survival, progression-free survival and toxicity as secondary outcomes. According to the "Response evaluation in solid tumors (RECIST) criteria" version 1.1, a partial treatment response is defined as "at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters".[17] However, the RECIST criteria have not (yet) widely found their way in the field of PGLs. Therefore, it was decided not to restrict inclusion of studies to RECIST criteria only for tumor response.

To accurately assess response rates, only studies determining treatment response (tumor volume) by radiologic imaging were eligible for inclusion. Furthermore, only studies reporting a population of five or more PGL/PCC-patients were included, in order to avoid the inclusion of cases or case series which might be prone to selection and publication bias. In case of multiple studies describing the same cohort, the study which comprised the highest number of subjects and/or the longest duration of follow-up was included. Eligible studies were restricted to languages familiar to the authors (English, French, German and Dutch). When reported data were not sufficient for accurate data-extraction, we tried to contact the authors for clarification.

Search strategy

In October 2013 PubMed, MEDLINE, EMBASE, Web of Science, COCHRANE, CINAHL, Academic Search Premier and ScienceDirect were searched to identify potentially relevant studies (search strategy provided upon request). References of key articles were assessed for additional relevant articles.

Data extraction

All studies obtained from the search strategy were entered into reference manager software (Reference Manager version 12, Thomson Reuters, Philadelphia, PA) and were screened on title and abstract. Potentially relevant studies were retrieved for detailed assessment. For eligible studies, data were independently extracted by two reviewers (NN and GA).

Disagreements between reviewers were resolved by consensus, but when doubt remained, a third reviewer (EC) decided.

Risk of bias assessment

The present meta-analysis is based on observational studies. Risk of bias assessment was based on study components that potentially bias an association between the intervention under study (combination of chemotherapy with CVD) and the primary outcome (tumor volume). The following elements were assessed for all studies:

1. Risk of selection bias. Inclusion of consecutive exposed patients or a random sample of the inception cohort was considered a low risk of bias.
2. Adequacy of reporting of intervention (chemotherapy). When dose per cycle and number of cycles of chemotherapy were reported, this was considered adequate.
3. Adequacy of measurement of tumor volume. The effect of chemotherapy on tumor volume should have been measured by either MRI or CT scanning.
4. Adequate definition of tumor response. A prespecified definition of objective tumor response was considered adequate.
5. Adequacy of follow-up. Loss to follow-up < 5% was considered to represent a low risk of bias.

Statistical analysis

The main outcome of the present meta-analysis was the pooled percentage of PGL/PCC-patients with tumor response after CVD chemotherapy. The pooled percentage of PGL/PCC-patients with biochemical response after CVD chemotherapy was the secondary outcome. For all studies, the percentage of PGL/PCC-patients with tumor response was calculated as the number of PGL/PCC-patients with tumor response divided by the total number of PGL/PCC-patients treated with CVD chemotherapy. The same procedure was applied to the proportion of PGL/PCC-patients with biochemical response. For all percentages exact 95% confidence intervals (95% CI) were calculated.

Meta-analysis was performed using an exact likelihood approach. The method used was a logistic regression.[18] We considered a random-effects regression analysis by default, unless less than 5 studies contributed to a certain endpoint, because the between study variance can then not be assessed reliably. In such a case a fixed effect analysis was performed. For meta-analysis of proportions, the exact likelihood approach based on a binomial distribution has advantages compared to standard models based on normal distributions.[19] Firstly, estimates from a binomial model are less biased than estimates from models based on a normal approximation.[20] This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells. All analyses were performed with STATA 12.0 (Stata Corp, Texas, USA).

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Results

Study selection

The initial search resulted in 459 unique records; 12 were selected for detailed assessment (Figure 1). After detailed assessment, 6 articles were excluded for the following reasons: outcome other than tumor response ($n = 2$), no original data ($n = 1$) and the number of PGL/PCC-patients did not exceed five ($n = 3$). Furthermore, 2 studies comprised a cohort also described in another publication; the studies with the smallest sample sizes were excluded.[14,21] No new articles were found in references of key articles. Finally, a total of 4 studies were included in the present analysis, all written in English.[22-25]

Study characteristics

Study characteristics are displayed in Table 1. Included studies were published from 2008 to 2013. All included studies were classified as cohort studies.[26] A total of 50 patients were included in this meta-analysis. The largest study contained 18 subjects. Mean age of included patients ranged from 34 to 47 years.
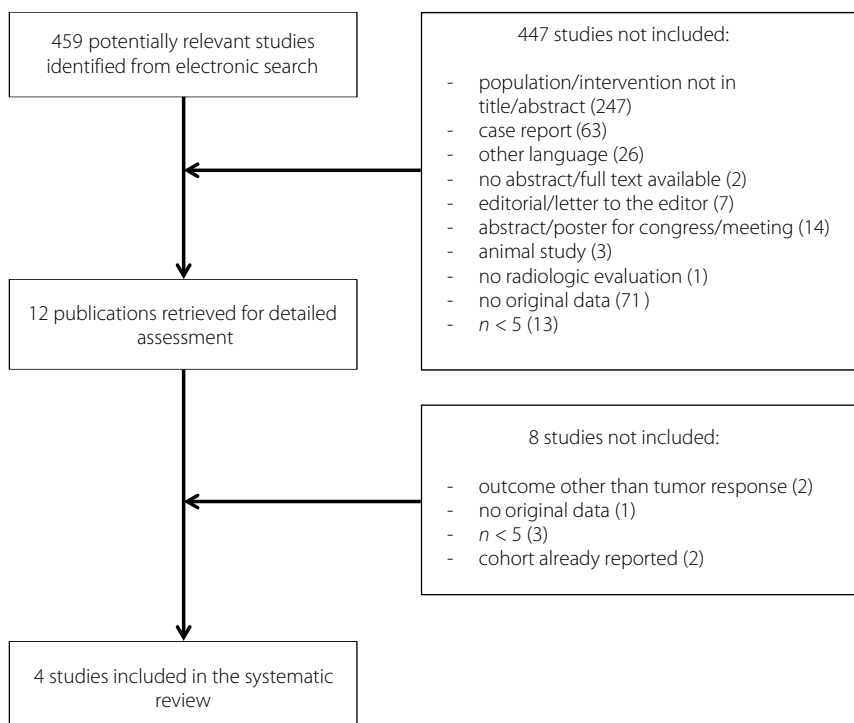

Figure 1. Flow-diagram of search strategy and study selection.

Risk of bias assessment

Summary characteristics of the risk of bias assessment are shown in Table 2. In all 4 studies included patients were explicitly described as consecutive exposed patients or as a random sample of the inception cohort. The intervention under study (i.e. CVD chemotherapy) was adequately described in 2 studies (50%). The effect of therapy on tumor volume was adequately measured (i.e. by CT and/or MRI) in all 4 studies. One study did not report prespecified definitions for assessment of tumor response. Actual loss to follow-up was reported in 3 of 4 studies (75%). In 2 of these 3 studies, loss to follow-up exceeded 5%.

Effect of CVD chemotherapy on tumor volume

Table 3 gives an overview of reported outcomes after CVD chemotherapy. To assess tumor response, one study used the RECIST criteria[24] and one study the RECIST 1.1 criteria.[25] One study used its own modified standard criteria[23] and one study did not report how tumor response was assessed.[22] Percentages of complete response after CVD chemotherapy ranged from 0% to 11%. For partial response, this was 24% to 50% and for stable disease 0% to 24%.

Results of the fixed effects meta-analysis are displayed in Figure 2. Pooled percentages of complete response, partial response and stable disease were 4% (95% CI: 1%-15%), 37% (95% CI: 25%-51%) and 14% (95% CI: 7%-27%), respectively.

Effect of CVD chemotherapy on catecholamine excess

Hormonal response was measured by only two studies. These two studies did not use standard criteria. The criteria used by the two studies are outlined in the appendix of Table 3. Percentages of complete response were 12% and 17%, partial response 24% and 55% and stable disease 17% and 24%.

The fixed effects meta-analysis resulted in pooled percentages of complete response, partial response and stable disease of, respectively, 14% (95% CI: 6%-30%), 40% (95% CI: 25%-57%) and 20% (95% CI: 10%-36%) (Figure 3).

Survival and side-effects of CVD chemotherapy

Information about survival and side-effects was only reported in three studies (Table 3). Side-effects comprised mainly gastrointestinal toxicity and myelosuppression.

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Tabel 1. Study characteristics of included studies

First author (year)	Number of patients (n)	Mean age ± SEM (range)	Primary tumor localization (PGL/PCC) (n)	Prior treatment (n)	Dose of chemotherapy	Number of chemotherapy cycles (mean ± SEM)	Imaging modality	Tumormarkers	Treatment evaluation	Genetical analysis	Mean ± SEM duration of f-up (months) (range)	Loss of f-up (n+ reason)
Huang (2008)[23]	18	33.5 ± 3.4[a] (6-64)	PGL 9 PCC 9	Radiotherapy (6)	Cyclophosphamide 750 mg/m2[b], day 1 Vincristine 1.4 mg/m2, day 1 Dacarbazine 600 mg/m2, day 1 and 2 Every 21 to 28 days.	Patients whose tumors were scored as CR or PR: 27.4 ±5.5 cycles, median 23. Patients whose tumors did not respond: 8.75, median 5.5.	CT/^{131}I-MIBG	Urinary catecholamines, MN and VMA	Laboratory tests were repeated every 3-4 weeks throughout the treatment. Radiology and nuclear medicine studies were repeated every 6 to 16 weeks, if the original studies were abnormal	Presumed mutation: SDHB (3) Possible SDHB (2) SDHB or SDHD (4) SDHD confirmed (1)	Median potential follow-up 22 years	1, after 5 years, reason n.r.
Szalat (2011)[24]	5	39.2 ±5.5[c] (20-51)	PGL 1 PCC 4	Surgical resection (5) MIBG (1)	Cyclophosphamide, vincristine, dacarbazine[d]	Only reported for 2 patients; one had 6 courses and one 7 courses.	CT/MRI/^{18}F-FDG-PET/^{18}F-PET/^{123}I-MIBG	Urinary E, NE, NMN, MN Blood CgA	Tumor response to therapy was based on clinical, biochemical, and imaging studies available in patients'files, n.s.	No systematic molecular genetic testing	n.r.	n.r.
Ayala-Ramirez (2012)[22]	10[e]	47.0 ± 3.9 (33-70)	PGL 5 PCC 5	Only reported for all patients. ^{131}I-MIBG (2)	Cyclophosphamide 600-750 mg/m2 Vincristine 1-2 mg/m2, Dacarbazine 750-1000 mg/m2.	Median 9.0	CT/MRI	n.r.	Responses were categorized as the best response during the first chemotherapy regimen	Unknown (7) SDHB and SDHD negative (1) SDHB/SDHC/SDHD negative (1) Ret negative (1)	n.r.	0

Tabel 1. Study characteristics of included studies *(Continued)*

First author (year)	Number of patients (n)	Mean age ± SEM (range)	Primary tumor localization (PGL/PCC) (n)	Prior treatment (n)	Dose of chemotherapy	Number of chemotherapy cycles (mean ± SEM)	Imaging modality	Tumormarkers	Treatment evaluation	Genetical analysis	Mean ± SEM duration of f-up (months) (range)	Loss of f-up (n+ reason)
Tanabe (2013)[25]	17f	At initiation of CVD 54.6±12.6 (mean±SD) At diagnosis of PCC/ PGL: 41.3±17.6	PGL 13 PCC 4	n.r.	Cyclophosphamide 750 mg/m2 on day 1, vincristineg 1.4mg/m2 on day 1, dacarbazine 600mg/m2 on day 1 and 2 every 21-28 days.	n.r.	CT/MRI/ 123I-MIBG or 131I-MIBG	Plasma and urinary NE, plasma CgA	Imaging modalities were performed before and after CVD chemotherapy, not further specified.	Germline mutation testing was not performed in any of the patients	median 60 months, range 12-192 months	6f

Abbreviations: *n.r.* not reported; *n.s.* not specified; *PCC* pheochromocytoma; *PGL* paraganglioma; *CT* computed tomography; *MRI* magnetic resonance imaging; *131I-MIBG* 131Iodine-metaiodobenzylguanidine; *123Iodine-MIBG* 123Iodine- metaiodobenzylguanidine; *18F-FDG-PET* [18F]-fluorodeoxy-D-glucose positron emission tomography; *18F-DOPA-PET* [18F]-fluorohydroxyphenylalanine positron emission tomography; *E* epinephrine; *NE* norepinephrine; *DA* dopamine; *MN* metanephrines; *NMN* normetanephrines; *VMA* vanillyl mandelic acid; *CgA* chromogranin A; *SDHB* succinate dehydrogenase subunit B gene; *SDHC* succinate dehydrogenase subunit C gene; *SDHD* succinate dehydrogenase subunit D gene.

a Age at diagnosis.

b Initially, cyclophosphamide doses were escalated; however, if a patient had a nadir absolute neutrophil count less than 0.5x10⁹/L on 3 measurements or a platelet count less than 25x10⁹/L, the dose in the subsequent cycle was reduced 20% to 50%. The chemotherapy dose administered as a percentage of that planned was 80.0%, 74.7%, and 80.7% for cyclophosphamide, vincristine and dacarbazine respectively, in those whose tumors were scored as complete response or partial response, and 81.3%, 78.4% and 93.4% in those without a tumor response or with only minimal shrinkage.

c Age at first diagnosis.

d One patient received a therapeutic dose of mitotane to enhance the cytotoxic effect of chemotherapy.

e 54 patients received different chemotherapy regimens, 52 patients had their response status recorded, 10 patients received chemotherapy with cyclophosphamide, vincristine and dacarbazine. 19 patients received cyclophosphamide, vincristine, dacarbazine and doxorubicin, 12 patients received cyclophosphamide, doxorubicin and dacarbazine, 2 patients received cyclophosphamide, vincristine and doxorubicin, 1 patient received cyclophosphamide and doxorubicin, 1 patient CHOP, 1 patient Imatinib, 1 patient cisplatin and etoposide, 1 patient doxorubicin, vincristine and dacarbazine, 1 patient cyclophosphamide, vincristine and temozolomide, 1 patient carboplatin, etoposide and ifosfamide, 1 patient tamoxifen and 1 patient temozolomide, bevacizumab and sorafenib. Some data were only reported for the whole group of 52 patients.

f Originally, 23 patients received chemotherapy. Three patients were excluded from the analyses because of inadequate follow-up. CVD chemotherapy was discontinued in three cases because of poor general condition or adverse events (e.g., severe bone marrow suppression and liver dysfunction).

g The dosage of vincristine was limited to 2.0 mg/m2 body surface area/day according to an official instruction of the medicine in Japan. The treatment intervals were modified to 60-90 days in some patients after the 5th cycle for personal reasons (e.g. work schedule and economic factors).

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Table 2. Risk of bias assessment of included studies

First author (Year of publication)	Consecutive patients or random sample of inception cohort	Determination of intervention adequately reported	Adequate measurement of tumor response	Adequate definition of tumor response	Number of patients lost to follow-up (%)
Huang (2008)[23]	Yes	Yes	Yes	Yes	1 (5.5%)
Szalat (2011)[24]	Yes	No[a]	Yes	Yes	n.r.
Ayala-Ramirez (2012)[22]	Yes	Yes	Yes	No[b]	0 (0%)
Tanabe (2013)[25]	Yes	No[c]	Yes	Yes	6 (26%)[d]

a Dose and number of cycles not reported.
b Response by tumor size was defined as any objective reduction in the size of the tumor on cross-sectional imaging studies during the first chemotherapy regimen. No definition of progressive disease.
c Number of cycles not reported.
d Three cases were excluded because of inadequate follow-up. CVD chemotherapy was discontinued in 3 cases because of poor general condition or adverse effects (e.g. severe bone marrow suppression and liver dysfunction).

Table 3. Outcomes of CVD chemotherapy

First author (year)	Number of patients (n)	Response on imaging			Response hormonal			Overall survival time/rate (confidence interval)	Progression-free survival time/rate (confidence interval)	Toxicity (n)	Toxicity grading system
		Complete response (n)	Partial response (n)	Stable disease (n)	Complete response (n)	Partial response (n)	Stable disease (n)				
Huang (2008)[23]	18	2 (11%)[a]	8 (44%)[b]	3 (17%)[c]	3[d] (17%)	10 (55%)	3[c] (17%)	Median survival for all patients from on-study date: 3.3 years. Median survival from date of diagnosis 6.5 years. Median survival from the landmark date: 3.8 years for patients whose tumors had a CR or PR to chemotherapy and 1.8 years for the rest[e].	Median duration of reponse: 20 months	Myelosuppression, peripheral neuropathy and gastrointestinal toxicity (n.s.) 4 episodes of hypotension in the first 3 cycles of treatment.	n.r.
Szalat (2011)[24]	5	0[f]	1 (25%)	0	n.r.	n.r.	n.r.	n.r.	n.r.	Only reported that one patient had severe myelotoxicity.	n.r.
Ayala-Ramirez (2012)[22]	10	0[g]	5 (50%)	0	n.r.	n.r.	n.r.	31.5 months for responders and 24.1 months for nonresponders[h]	n.r.	n.r.	n.r.

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Table 3. Outcomes of CVD chemotherapy (*Continued*)

First author (year)	Number of patients (n)	Response on imaging				Response hormonal				Overall survival time/rate (confidence interval)	Progression-free survival time/rate (confidence interval)	Toxicity (n)	Toxicity grading system
		Complete response (n)	Partial response (n)	Stable disease (n)		Complete response (n)	Partial response (n)	Stable disease (n)					
Tanabe (2013)[25]	17	0[i]	4 (24%)[j]	4 (24%)		2[k] (12%)	4 (24%)[l]	4 (24%)		50% survival was 6 years in the patients with complete or partial biochemical and/or partial tumor response (n=8), and 4 years in the patients with no significant biochemical or tumor reponse (n=4), and 3 years in the patients with deterioration in biochemical and tumor responses (n=5)	Median 40 months, range 31-60 months	Grade 3 gastro-intestinal symptoms with discontinuation of CVD (1) Grade 2 leukopenia with discontinuation (1) Grade 2 liver dysfunction with discontinuation (1) Leukopenia grade 2 and liver dysfunction grade 1 lasting for up to 1 week after each CVD cycle Gastro-intestinal symptoms grade 2 and high fever grade 1 (transient and mild)	Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0[m]

Abbreviations: *n.s.* not specified; *n.r.* not reported.

a Tumor response defined as: complete response (CR); complete regression of all clinical evidence of disease; partial response (PR); at least 50% reduction of all measurable tumor; minimal response (MR); at least 25% but not more than 50% reduction of all measurable tumor; no change (NC); progressive disease (PD): appearance of a new lesion or an increase of 25% of any measurable tumor.

b Also 3 patients (17%) with MR.

c Five patients reported with "no response," including patients with NC ánd PD. Because 14 of the 18 patients in this study were already reported by Averbuch *et al.* in 1988[14], and extracted data about NC and PD from those 14 patients were available, we extrapolated those data. For tumor reponse and for biochemical response, Averbuch *et al.*[14] reported 2 patients with NC and 1 patient with PD and Huang reported 5 patients with NC ánd PD. Therefore we extrapolated that there were 3 patients with NC and 2 patients with PD.

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d Biochemical response defined as: CR: normal values; PR: at least a 50% reduction; MR: at least 25% but not more than 50% reduction; no change; PD: an increase of at least 25%, in all three measurements.

e Landmark date: 3 months after starting chemotherapy. Difference not statistically significant (p = 0.65).

f Response according to RECIST criteria.[31] Response only reported for 4 patients.

g Response by tumor size was defined as any objective reduction in the size of the tumor on cross-sectional imaging studies during the first chemotherapy regimen. Responses were categorized as the best response during the first chemotherapy regimen.

h Landmark time: 1 year from the start of chemotherapy. P-value 0.79.

i Tumor response according to RECIST 1.1 guidelines[17] and the standard criteria described by Averbuch et al.[14] Tumor response was classified as follows: CR: disappearance of all measurable tumor; PR: >50% tumor reduction; MR >25% but <50% tumor reduction; stable disease: no significant change in tumor; PD: the appearance of new lesion(s) or increased size >20% of total target lesions.

j Also 4 patients (24%) with MR.

k Biochemical response according to modified the criteria by Averbuch et al.[14] Biochemical response was classified as follows: CR: normalization of the biochemical tumor markers; PR: >50% reduction; MR: >25% and <50% reduction; NC: <25% reduction and <25% increase; PD: >25% increase of the biochemical tumor markers.

l Also 2 patients (12%) with MR.

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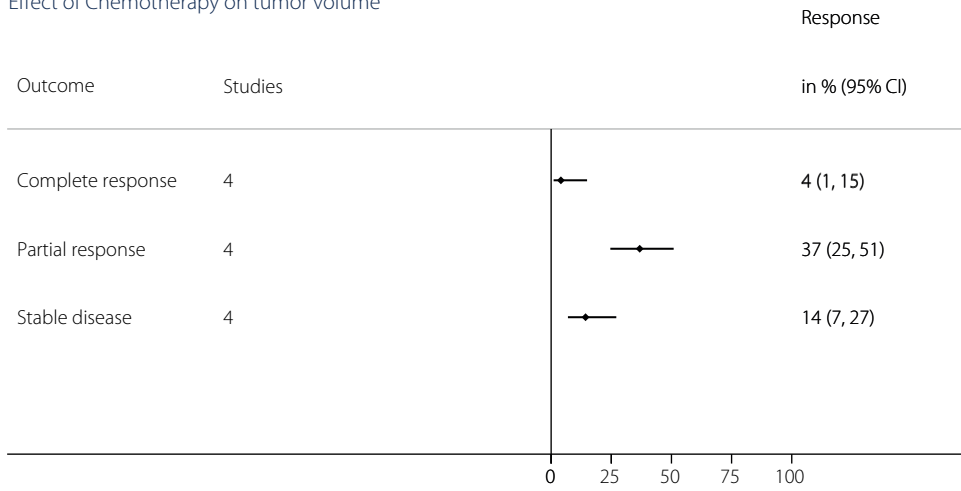
Effect of Chemotherapy on tumor volume

Outcome	Studies		Response in % (95% CI)
Complete response	4		4 (1, 15)
Partial response	4		37 (25, 51)
Stable disease	4		14 (7, 27)

Figure 2. Effect of chemotherapy on tumor volume.

Effect of Chemotherapy on Cathecholamine excess

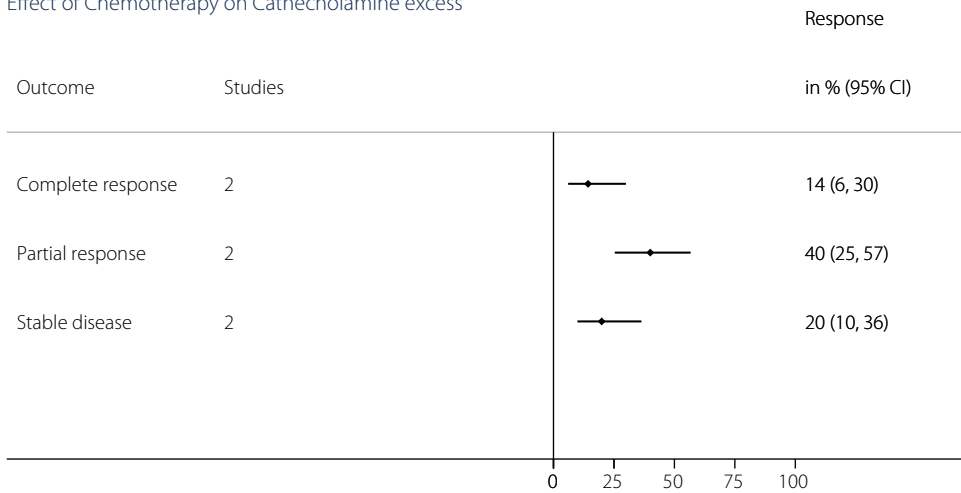| Outcome	Studies		Response in % (95% CI)
Complete response	2		14 (6, 30)
Partial response	2		40 (25, 57)
Stable disease	2		20 (10, 36)

Figure 3. Effect of chemotherapy on catecholamine excess.

Discussion

The present systematic review and meta-analysis aimed to assess tumor response and hormonal overproduction of malignant PGL/PCC after CVD chemotherapy. Our meta-analysis showed that partial response on tumor volume following CVD chemotherapy could be achieved in about 37% of the patients and a partial hormonal response in about 40%. Complete response on tumor volume could be achieved in only 4% of patients. Toxicity leading to discontinuation of therapy was reported several times. With the results of this study, it is possible to inform both patients with malignant PGL/PCC and their treating physicians more adequately concerning the expected tumor response and the effect on survival after CVD chemotherapy.

In the included studies, the protocol when to initiate treatment was not well described. Only one study included patients with progressive metastatic disease; however, a definition of progression was not given.[22] The other three studies did not describe whether there was evidence of progressive disease. Hescot *et al.* recently published a study in which the natural history of patients with malignant PGL/PCC was assessed.[27] They found that half of the patients with metastatic PGL/PCC have stable disease at 1 year without any intervention. Therefore, they recommended a wait-and-see policy as first line management in asymptomatic patients with malignant PGL/PCC.[27] With regard to the results of our review, it can not be excluded that the reported effect of chemotherapy on tumor volume reflects the natural course of the disease, at least partially. CVD chemotherapy is a therapy regimen with potentially serious side effects like myelosuppression. Therefore it is important to realize that a wait-and-see policy might be a better option in asymptomatic patients.

Our meta-analysis showed that a partial response concerning catecholamine excess could be achieved in 40% of patients. This is a meaningful finding because reduced tumor function and, as a consequence, symptom palliation is an important treatment goal in patients with malignant PGL/PCC. Because quality of life was not an endpoint in the included studies, the question remains if the reduction in tumor function will lead to a better quality of life. Future studies with quality of life as an endpoint may probably point this out.

There are some limitations that should be taken into account when interpreting this meta-analysis. We could include only four studies with a total of 50 patients and only two studies reported effects of CVD therapy on catecholamine excess. This is, however, inevitable in view of the extremely low prevalence of malignant PGL/PCC. This means that results should be interpreted with caution as the reported effects may not be precise. In addition, because of the limited number of patients, a separate meta-analysis for PCC and PGL patients was not possible. Also, it would be of interest to assess responsiveness in different groups, for example men *vs* women, high *vs* low Ki67 index and presence or absence of a genetic syndrome, however, due to the low number of patients included in our meta-analysis, a

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separate analysis for these different groups would lack statistical power.

We cannot rule out that the four cohorts listed might be different from each other concerning, for example progressiveness of the disease. Prior treatment regimen differed between 3 studies and was not reported in the other study. This difference in prior treatment regimen might be the result of more or less aggressive tumors in the included patients. This should be taken into account when interpreting these results.

Of the four included studies, two studies used RECIST and RECIST 1.1 criteria to assess tumor response. In one study, there was no adequate definition of tumor response[22] and another study used its own criteria.[23] Because of this heterogeneity, it is more difficult to compare the studies objectively. This may have contributed to differences in response rates. Also, when interpreting the data, it should be kept in mind that the analysis is based on four studies only, and that these four studies show clinical heterogeneity.

More recently, studies assessing targeted therapies, such as Sunitinib, have shown promising results in the treatment of malignant PGL.[28] Sunitinib is an oral tyrosine kinase inhibitor with antiangiogenic and antitumor activity. Currently, the published data are limited to only a few case reports and retrospective reports,[28-30] but a single arm open-label phase II trial with sunitinib is currently underway with an estimated study completion date of December 2013 (clinicaltrials.gov). Also, a first international, randomized, double blind, phase II, multicenter study has started in December 2011. This study aimed to determine the efficacy of Sunitinib on the progression-free survival at twelve months in subjects with progressive malignant PCC and PGL. The estimated study completion date of this study is December 2019 (clinicaltrials.gov).

In conclusion, with CVD chemotherapy a partial response concerning tumor volume can be achieved in about 37% of patients and a partial response on catecholamine excess in about 40% of patients with malignant PGL/PCC. However, the possibility remains that the reported effect on tumor volume reflects, at least partially, the natural course of the disease. Data are scarce and large clinical trials are lacking; therefore, more studies are needed to determine the precise effect of CVD chemotherapy.

Acknowledgements

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