Cisplatin and cerebral infarction

Introduction

Cisplatin (Platosin®) is indicated for *the treatment of extensive or metastatic tumours: testicular carcinoma (palliative and curative therapy), ovarian carcinoma (stage III and IV) and squamous cell carcinoma of the head and neck (palliative therapy). Cisplatin can be used as monotherapy or in combination with other chemotherapeutic substances* [1].

Reports

Until December 8, 2007, the Netherlands Pharmacovigilance Centre Lareb received 12 reports of (specific symptoms of) cerebral infarction associated with the use of cisplatin. Reported terms were brainstem infarction, arterial thromboembolism, cerebral infarction, cerebrovascular accident, cerebrovascular disorder, embolism, hemiplegia, paralysis, and cortical blindness. Four of these reports were excluded because of lack of precise information on cerebral infarction or causality was not likely according to Lareb.

Of the eight remaining reports, seven were reported by the MAH and one by a medical specialist (report G). In four patients, the indication for cisplatin was non small cell lung carcinoma.
Latency time varies from 3 days up to 14 days, in six reports within a week after the last dose of cisplatin. All patients used additional chemotherapeutics. No risk factors were described in the reports

In patients B, C and E, the investigator in these study reports considered the ischemic event unlikely to the suspected medication. In patient F a CT scan of the brain revealed subcortical infarction in the left hemisphere and angiography revealed an almost complete thrombotic occlusion of the left carotid artery. Mild hypomagnesemia was found.

Table 1. Reports of cerebrovascular events associated with the use of cisplatin

Patient, Sex, age	Daily dose Indication for use	Other medication	Suspected adverse drug reaction	Time to onset after last dose, outcome
A M, 69	cisplatin 50 mg Indication unknown	gemcitabine*, tolbutamide, amlodipine, hydrochlorothiazide / triamterene.	cerebral infarction	14 days, drug withdrawn, outcome unknown
B V, 60	cisplatin, 70 mg/m2 ovarian cancer	topotecan*	cerebrovascular accident	6 days, recovered with sequel
C F, 68	cisplatin 140 mg/day Non small cell lung carcinoma	gemcitabine*, insulin, metformin, atorvastatin	nausea, vomiting and diarrhoea after 1st cycle, cerebral infarct after 2nd cycle	both episodes 5 days, patient died, autopsy showed intracranial embolisms and no brain metastases
D, F, 50	cisplatin, 110 mg (1^{st} cycle) non small cell lung	gemcitabine*	cerebrovascular accident, peripheral ischemia left leg,	4 days, drug withdrawn, recovering

Patient, Sex, age	Daily dose Indication for use	Other medication	Suspected adverse drug reaction	Time to onset after last dose, outcome
	carcinoma		nausea, vomiting	
E M, 56	cisplatin, 75 mg Non small cell lung carcinoma stage IIIa	docetaxel*, loperamide, granisetron	ischemic stroke	3 days, recovered with sequel
F M, 33	cisplatin 20 mg/ m^2 (2^{nd} cycle) testicular non-seminoma carcinoma	bleomycin, etoposide	two cerebral infarctions, myocardial infarction	6 days, chemotherapy withdrawn, revalidation.
G V, 65	cisplatin 160 mg (2nd cycle) non-small cell lung cancer, stage IIB	gemcitabine	cerebrovascular infarction, ischemic necrosis both feet, renal insufficiency	3 days, refrain from further treatment
H M, age unknown	cisplatin 15 mg, 200 mg/m^2 advanced penile carcinoma	bleomycin*, methotrexate*	brain stem infarction	14 days. patient died

* This drug was also suspected

Other sources of information

SmPC

In the SmPC of cisplatin Hexal [2] and cisplatin Eurocept [1], cerebral disorders (paralysis is mentioned) and vascular disorders (cerebral or myocardial ischemia is mentioned) are described. In the other SmPCs of cisplatin, cerebral infarction is not described.

Literature

There are several risk factors for coagulopathy caused by the malignancy, atherosclerosis, and pre-existing cardiovascular disease [3].
In addition, brain metastases in patients with non small cell lung cancer can induce symptoms similar to CVA in 25% of these patients. In approximately 5% of these patients a CVA can be detected by CT-scan [4].

Several cases of cerebral infarctions with the use of cisplatin are described in literature. One of these cases was also reported to the Netherlands Pharmacovigilance Centre Lareb (patient F) [5]. Six days after the second cycle of chemotherapy with bleomycin, etoposide and cisplatin, a 33-year old male had a myocardial infarction and a cerebral infarction followed by a second cerebral infarction 2 days later. Mild hypomagnesaemia was diagnosed. After adequate treatment and clinical improvement the patient was transferred to a rehabilitation centre, chemotherapy was withdrawn.

In another case report, a 21-year old female with mixed germ cell tumour was given bleomycin, etoposide and cisplatin. During the second cycle, she complained of dizziness. After the third cycle, she had a left-sided total anterior cerebral infarct, confirmed on MRI. This patient was a non-smoker with no risk factors for

cardiovascular diseases, like hypertension or hypercholesterolemia. Her coagulation profile and electrolytes were normal. The patient recovered [6].

A third case report concerns a 29-year old female who received S-1 (a 5-fluorouracil derivate) and cisplatin for gastric carcinoma. On day 15 of the first cycle she experienced dizziness and transient paralysis of the fingers of both hands. On day 13 of the second cycle, the patient developed an acute ischemic cerebral infarction of the left cerebral hemisphere. Plasma protein C and serum magnesium levels were decreased and plasma von Willebrand factor was elevated. The patient did not have any risk factors like hypertension, hypercholesterolemia, diabetes mellitus, or smoking. Coagulation markers were normal [7].

In a retrospective study by Li *et al.* [3] data from a cancer database were analysed. The incidence for ischemic stroke in patients receiving chemotherapy was 0.137% (15 patients and 16 ischemic strokes out of 10,963 patients). Most of these patients had a latency of 10 days or less after the latest chemotherapy session, which suggests a direct effect of the chemotherapeutic drug. Platinum based chemotherapy was the most common regimen prior to stroke (9 out of 16). Renal excretion of cisplatin is almost complete within 10 days after administration. In a minority of patients, ischemic strokes occurred 21-30 days after the latest cycle. This suggests a role for metabolites of the drug [3].

Mechanism

Cisplatin increases the risk of thrombotic disorders, but the exact mechanism remains unknown. Several factors, like hypercoagulability and vasospasms due to hypomagnesaemia can be responsible [5].
Cisplatin causes hypomagnesaemia in 76 to 87% of the treated patients. This is due to a decreased renal tubular reabsorption [8]. Low magnesium levels increase intracellular calcium concentration, initiating smooth muscle contraction causing vasospasm and tissue ischemia [5-7]. Hypomagnesaemia is listed in the SmPC of cisplatin [1].
Vascular toxicity caused by the chemotherapy itself can also increase the risk of stroke. Destruction of tumour cells by chemotherapy can cause mucin influx into the circulation through which hypercoagulation may occur [7].

Databases

On December 8, 2007, the Lareb database contained eight reports of cisplatin and cerebral infarctions which is disproportional (ROR 5.1, 95% CI 2.5-10).

On December 8, 2007, the WHO Collaborating Centre had received three reports of cerebellar infarction (ROR 20, 95% CI 6.2- 63), 42 reports of cerebral infarction (ROR 4.7, 95% CI 3.6- 6.4) and seven reports of cerebral ischemia (ROR 2.8, 95% CI 1.3- 5.9). All these reports are disproportionally present in association with cisplatin. In addition, the WHO Collaborating Centre received 86 reports of cerebrovascular disorder with the use of cisplatin (ROR 1.2, 95% CI 1.0-1.5) but it is unknown if these events concerned infarction or bleeding.

Discussion

In literature, several papers describe cerebral ischemia induced by cisplatin, but the role for risk factors for thromboembolism like atherosclerosis and pre-existing cardiovascular diseases cannot be excluded [3]. In the cases reported to Lareb, only three out of eight patients in table 1 used cardiovascular medication.

Brain metastases in patients with non small cell lung cancer can also induce CVA-like symptoms. Brain metastases are primarily caused by pulmonary carcinoma, melanoma, and mamma carcinoma [4]. In the cases reported to Lareb, four concerned pulmonary carcinoma and the indication of one report was not further specified, therefore brain metastases could have caused the symptoms. On the other hand, the temporal relationship with the use of chemotherapy does not make this alternative explanation plausible.

In addition, information from CT scan was available in two patients. In patient D no other explanation for the complaints was found and the cause was identified as thromboembolism. In patient F [5], CT scan showed a subcortical infarction. In patient C no CT or MRI is mentioned, but 'cerebral infarction, some evidence of embolism and no evidence of metastatic spread to the brain' was reported.

Li *et al*. [3] describe the incidence of ischemic stroke during one month post-chemotherapy. Our reports are consistent with their findings that a majority of the strokes occurred within 10 days after start of the chemotherapy and occurred after the first cycle.

All patients in the reports to Lareb used cisplatin in combination with other suspect chemotherapeutic drugs. For gemcitabine, myocardial infarction is labelled. For bleomycin, myocardial infarction, coronary heart disorder, and bleeding disorders in the brain are described. For topotecan, no relevant conditions are labelled. Cisplatin was the common factor in these reports and the chemotherapy protocols were not similar in all reports, therefore an association with cisplatin is suspected.

In the Netherlands, most cancer patients are treated in a clinical research protocol, so reports on chemotherapy to Lareb are mainly study reports.

Conclusion

Lareb received eight reports of cerebrovascular accidents and arterial thromboembolism associated with the use of cisplatin. Cerebral ischemia is not described in all SmPCs of cisplatin. Although confounding factors like malignancy and concomitant medication can not be excluded, the number of reports is remarkably high. Cerebral ischemia associated with the use of cisplatin is also described in literature, with a possible mechanism due to hypomagnesiemia and vascular toxicity.

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