Cisplatin and peripheral arterial thromboembolic events

Introduction

Cisplatin (generic, Platosin®) is the first member of the platinum-containing anti-cancer drugs and internationally introduced in 1979. Cisplatin is indicated for the treatment of extensive or metastatic tumors like testicular carcinoma, ovarian carcinoma, squamous cell carcinoma of the head and neck, bladder carcinoma, small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). Cisplatin can be used as monotherapy or in combination with other chemotherapeutic substances like e.g. etoposide, bleomycin or paclitaxel [1,2]. Cisplatin exerts its cytotoxic effect by forming structural different adducts with DNA. This DNA cross-linkage cause irreparable damage resulting in cell death. The adverse drug reactions (ADRs) are dose related and can be cumulative [2].
The most common ADRs are haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal disorders (anorexia, nausea, vomiting, diarrhoea), ear disorders like hearing impairment, renal disorders (renal failure, nephrotoxicity, hyperuricemia) and fever [1].
Cancer patients are known to have an increased risk of venous and arterial thromboembolic events (VTEs/ATEs). Several factors influence the risk, including age, type/site cancer, smoking, hospitalization and indwelling catheters. In addition, chemotherapy could contribute to this risk as well. Especially cisplatin-based chemotherapy (CBC) has been associated with a wide range of thromboembolic complications. CBC is even associated with a 1.67-fold increased risk for venous thromboembolic events compared with non–cisplatin-based chemotherapy (p=0.01, RR 1.67 (95% CI 1.25-2.23)) [3]. However, the occurrence of ATEs associated with CBC has been reported rarely, at all if there no further risk factors are present. The Dutch SmPCs for cisplatin already mentions the arterial events myocardial infarction and cerebrovascular accident. The SmPC of Platosin® and cisplatin from the brand PCH and Teva mention an occlusion of the arteria carotis as well [1,4,5]. The current observation describes the association between cisplatin and peripheral ATEs.

Netherlands Pharmacovigilance Centre Lareb
In the period from December 23rd 1996 until September 1th 2015, the Netherlands Pharmacovigilance Centre Lareb received 16 reports of peripheral ATEs, namely 9 of arterial occlusive disease, 1 of arterial embolism, 4 of peripheral artery thrombosis, 1 of ischemic necrosis and 1 of peripheral arterial occlusive disease. The details of the received reports are presented in table 1. Besides the reports of peripheral ATEs, Lareb received as well 1 report of arterial thrombosis of the aorta and left artery renalis and several reports of myocardial and cerebral infarction [6]. In 2008 Lareb already published a signal about cisplatin and cerebral infarction [7]. This signal focusses on peripheral ATEs.

Table 1. Reports of peripheral arterial thromboembolic events associated with the use of cisplatin based chemotherapy.

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 188431, F, 61-70 years, pharmacist	cisplatin, 1 mg/ml, NSCLC	temazepam, salbutamol, simvastatin, tramadol/paracetamol, pemetrexed	peripheral artery thrombosis	6 days, drug withdrawn, not recovered
B, 186099, M, 61-70 years,, pharmacist	cisplatin 0,5 mg/ml, lung cancer pemetrexed, lung cancer		arterial occlusive disease	unknown, drugs withdrawn, recovered with sequel
C, 182380, M, 41-50 years, pharmacist	cisplatin 0,5 mg/ml		arterial occlusive disease	6 weeks, unknown, recovering
D, 158958, F, 41-50 years, MAH	cisplatin 1 mg/ml, bladder carcinoma	gemcitabine, metformin	arterial occlusive disease	41 days, drug withdrawn, recovered with sequel
E, 160832, M, 51-60 years, MAH	BEP chemotherapy, seminoma		peripheral artery thrombosis (3x), pulmonary	49/39 days, unknown, unknown

			embolism	
F, 126011, F, 51-60 years, physician	cisplatin 1 mg/ml, SCLC		arterial occlusive disease, necrosis ischaemic	5 days, no change, recovered with sequel
G, 117684, M, 51-60 years, physician	cisplatin 1 m/ml, lung carcinoma	gemcitabine	arterial occlusive disease	5 days, unknown, recovering
H, 132487, M, MAH	cisplatin 10 mg, unknown	pemetrexed	arterial occlusive disease	unknown, drug withdrawn, recovered
I, 132458, M, MAH	cisplatin 10 mg, unknown	pemetrexed	arterial occlusive disease	unknown, drug withdrawn, unknown
J, 132235, M, MAH	cisplatin 10 mg, unknown	pemetrexed	peripheral arterial occlusive disease	unknown, drug withdrawn, unknown
K, 132459, F, MAH	cisplatin 0,5 mg/ml, unknown	pemetrexed	arterial occlusive disease	unknown, drug withdrawn, unknown
L, 132579, M, MAH	cisplatin 0,5 mg/ml, unknown	etoposide	arterial occlusive disease	unknown, drug withdrawn, unknown
M, 102727, F, 51-60, physician	cisplatin 0,5 mg/ml, lung carcinoma gemcitabine, lung carcinoma	metoclopramide, ibuprofen, granisetron, budesonide/formoterol, insulin detemir, insulin glulisine	necrosis ischaemic	56 days, drugs withdrawn, unknown
N, 40756, M, 21-30 years, physician	BEP chemotherapy, testis carcinoma ondansetron 2 mg/ml	olanzapine	peripheral artery thrombosis	unknown
O, 30616, M, 61-70 years, MAH	cisplatin 1mg/ml, NSCLC gemcitabine, NSCLC	omeprazole, ibuprofen, losartan	arterial embolism	22 days, drugs withdrawn, recovered
P, 26062, M, 61-70 years, MAH	cisplatin 1 mg/ml, unknown gemcitabine 200 mg, Unknown		peripheral artery thrombosis, peripheral coldness	unknown

Report A

The patient stopped smoking 2 years prior to this event, but her husband is still smoking. At the age of 36 the patient underwent angioplasty of the aorta. The patient had no metastases. The patient has a BMI of 21 kg/m^2. The use of simvastatin could indicate confounding by indication. According to the reporter the patient suffered from a painful and white colored foot 6 days after the first administration of cisplatin and pemetrexed. The patient went to the emergency room and the symptoms were diagnosed as Raynaud's phenomenon. Five days later the patient went again to the emergency room because the foot was still white and more painful. The patient was diagnosed with arterial thrombosis, was hospitalized and treated with heparin. One day after hospitalization the toes of the foot turned black and the foot was very painful. Five days after hospitalization the patient underwent amputation of the right leg. It seems that there was mention of a doctors' delay. At the day of amputation the patient had a high unspecified red blood cell count. Thirteen days after amputation the patient started with rehabilitation. One month after the amputation the patient was treated with carboplatin/pemetrexed for her NSCLC.

Report B/C

Both reports are from the same hospital. In patient B the arterial occlusion was located in the left forearm. The occlusion occurred after the first administration of cisplatin and pemetrexed. The patient received iloprost and the forearm was amputated. In report C the reporter mentioned that 1 year ago the oncology department had also two cases of arterial occlusion. These two patients died. Besides myocardial infarction and cerebrovascular accident no ATE are mentioned in the SmPC of pemetrexed.

Report D
The patient had in both legs an occlusion of three femoral arteries. The arterial occlusions occurred after the 2nd chemotherapy with cisplatin and gemcitabine. Both feet had to be amputated. The patient has type 2 diabetes mellitus and a BMI of 27 kg/m^2. It is unknown if the patient had vascular disease due to the diabetes mellitus. The SmPC of gemcitabine mentions the following ATEs or risk factors as ADR, arrhythmia, myocardial infarction, cerebrovascular accident and peripheral vasculitis.

Report E
The patient developed besides the pulmonary embolism, thrombosis of the iliac artery, femoral artery and popliteal artery. The patient has seminoma with metastases in abdominal lymph nodes. The patient underwent an unspecified surgery prior to the chemotherapy as well. Based on the reported dates the events occurred after the 2nd administration of the BEP chemotherapy. The arterial thrombosis appears 1 day after the last dose of cisplatin.

Report F
The patient was recently diagnosed with SCLC with a paraneoplastic cerebellar syndrome. The arterial occlusion and ischemic necrosis occurred after the first cisplatin treatment. The patient underwent an embolectomy and due to the necrosis her feet was amputated. The patient has a BMI of 22 kg/m^2. Further, the reporter mentions that in the past three years there were at least 8 cases of arterial occlusion with cisplatin chemotherapy. These cases could not be explained by cardiac arrhythmia and/or atherosclerosis.

Report G
The location of the arterial occlusion is not specified. The patient was treated with iloprost and heparin and is recovering. The patient has a BMI of 23 kg/m^2.

Report H to L
All reports are reported by the same hospital pharmacist. The reporter mentions an increase in vascular complications after transition from Platosin® to generic cisplatin. Patient H developed the occlusion is his leg, patient I in his right foot, patient J in his left foot, patient K in her right foot and patient L in his left leg. All patients underwent angioplasty.

Report M
The physician reports peripheral arterial ischemia. The ischemic feet occurred quit spontaneously after the 3rd administration of cisplatin and gemcitabine. The reporter sees no other conceivable explanation. CT-angiography reveals gracile large arterial vessels, but normal patency. The dermatologist suspects a peripheral arterial disorder due to cisplatin/gemcitabine therapy. The surgeon thinks the ischemic feet are a result of a paraneoplastic syndrome. Amputations of the toes might be necessary. The patient received enoxaparin and acetylsalicylic acid. Because of a CRP of 334 mg/l amoxicillin/clavulanic acid was started. The patient has insulin-requiring type 2 diabetes mellitus and COPD. The patient had no diabetic neuro- and/or angiopathy.

Report N
The physician reports bilateral arterial thrombosis legs after the 3rd administration of BEP chemotherapy (bleomycin, etoposide, cisplatin). The patient received unspecified anticoagulants and streptokinase and the right foot was amputated. Further the reporter mentions that cisplatin is known for its vascular complications, but he never seen this clinical outcome. Olanzapine is associated with an increased risk of venous thromboembolism and the reporter wonders if there could be a relation with the ATE.

Report O
The arterial embolism occurred in the patient's limb and after the 2nd administration of cisplatin and gemcitabine.

Report P
The patient experienced the arterial thrombosis and coldness in his leg.

Other sources of information

SmPC
The US SmPC of cisplatin and all the Dutch SmPCs for generic cisplatin and Platosin® mention the following vascular disorders, myocardial infarction, cerebrovascular accident, thrombotic micro-angiopathy (haemolytic-uremic syndrome) and Raynaud's phenomenon [8,9]. There is some discrepancy in information, because some of the SmPCs mention coronary artery disease (cisplatin Mylan) and occlusion of the artery carotis (Platosin®, cisplatin PCH/Teva) as well [1,4,5,10].

Literature
Despite the possible severe consequences of (peripheral) ATEs, the association with cisplatin and malignancy is not well studied. In a retrospective analysis by Mellema *et al*. 784 patients with NSCLC treated with platinum based chemotherapy were analyzed. Among these patients 24 patients developed an ATE (13 cerebral ischemic stroke, 6 myocardial infarction and 6 lower limb thrombosis). Risk factors like smoking, diabetes or hypertension had no significant relation with incidence of ATEs. All the 24 patients received CBC, except 1 patient received carboplatin. The difference in thromboembolic events incidence between carboplatin and cisplatin was not significant (p=0.42) [11]. Another retrospective study showed that among 932 patients with any type of cancer were treated with CBC, 19 patients (2%) developed an ATE (2 myocardial infarction, 10 cerebrovascular accident, 1 aortic arch, 3 infrarenal aortic, 1 internal carotid, 1 splenic artery and 1 superior mesenteric artery) [12].
A direct role of cisplatin in comparison with oxaliplatin, another platinum containing anticancer drug, is revealed in a randomized, controlled trial with 964 patients treated with epirubicin/platinum/fluor pyrimidine combination for advanced/locally gastroesophageal cancer. This study found a statistically significant difference in the incidence of ATEs between CBC and oxaliplatin based chemotherapy (2.9% versus 1.1%, respectively; p=0.044) [13].
In addition, case reports of peripheral ATEs associated with CBC in patients with gastric carcinoma, tongue carcinoma, germ cell tumor and lung cancer, are over the last 20 years widely published [14-16,16,17]. For example, arterial thrombosis of the radial artery, ulnar artery, iliac artery, femoral artery and popliteal artery were observed. Remarkable, is that in some cases risk factors like arrhythmia, vascular diseases, smoking are excluded. Thereby it seems that in some cases, like in Lareb report A, complaints like pain and discoloration are not immediately recognized as possible peripheral ATEs [16,17].
Interestingly as well are 5 cases described by Mathews *et al*. In all cases the patients had risk factors for ATEs, but looking to the timing of events, cisplatin could have an aggravating role. In all cases a peripheral ATE occurred shortly after the 1st or 2nd administration [17]. Off course the arterial thrombi in these patients may have been the result of natural progression of their vascular disease or the malignancy itself. But together with the possible described vascular toxicity and short latency time, potential causality cannot be ignored. The short timing of peripheral ATEs was also showed in 5 Lareb reports (report A, B, D, E, and O) and in a study from Numico *et al*. In this study 45% of the thromboembolic events occurred during the first 2 courses [18]. Thereby it appears that arterial events occur earlier then venous events. The median number of days after start of CBC was 35 for ATE and 61 for VTEs. Another interesting thought is the type of cancer in a case report from Cheng et al. and a retrospective study from Weijl et al [16,19]. In both all the patients received CBC for germ cell tumors. Patients with germ cell tumors are mostly younger than patient who are treated for other types of solid tumors and therefore have fewer cardiovascular risk factors. The occurrence seems thus more dependent on CBC and the malignancy.
However most of the evidence of this association is based on case reports and retrospective studies. Proverbs-Singh *et al.* performed a systematic review and meta-analysis of randomized controlled trials evaluating the incidence and risk of ATEs associated with CBC. CBC versus non-CBC were evaluated in patients with solid tumors. The incidence of ATE in patients receiving CBC was 0.67% (95% CI 0.40-0.95). The relative risk of ATEs for CBC versus non-CBC was not significant (1.36 95% CI 0.86-2.17)) [20]. The question is whether it is possible to achieve a clinical significance with this low incidence. None of the subgroup analysis of dose intensity, cisplatin or non-cisplatin, tumor site or publication year, were statistically significant. Moreover, in most studies VTEs and ATEs are often

analyzed as one group. Because of the higher incidence of VTEs, most statistic results are therefore driven by venous events. Lastly, intra-arterial cisplatin is a therapeutic option in treatment of hepatocellular carcinoma. Besides the lack of direct comparing evidence with systemic chemotherapy, vascular complication including hepatic arterial and catheter occlusion may occasionally occur [21]. In none of the described Lareb reports, studies and case reports cisplatin is administered via arterial infusion.

Databases

Table 2. Reporting odds ratios of cisplatin based chemotherapy and peripheral arterial thromboembolic events in the database of the Netherlands Pharmacovigilance Centre Lareb, the WHO and the Eudravigilance (EMA) database [6,22,23]. From the reports of the WHO and Eudravigilance database it is not known whether these are all peripheral of nature.

Drug and ADR	Number of reports	ROR (95% CI)
Arterial occlusive disease	Lareb: 9	184.7 (80.5-423.9)
	WHO: 15	1.4 (0.9-2.3)
	Eudravigilance: 19	3.1 (2.0-4.9)
Arterial embolism	Lareb: 1	11.6 (1.6-85.4)
	WHO: 25	7.4 (5.0-11.0)
	Eudravigilance: 8	7.7 (3.8-15.5)
Peripheral artery thrombosis	Lareb: 4	55.5 (19.0-161.5)
	WHO: 33	7.6 (5.4-10.8)
	Eudravigilance: 14	5.7 (3.3-9.7)
Peripheral arterial occlusive disease	Lareb: 1	40.5 (5.2-314.2)
	WHO: 11	2.0 (1.1-3.6)
	Eudravigilance: 6	1.6 (0.7-3.5)
Ischemic necrosis	Lareb: 3	152.3 (38.0-610.3)
	WHO: 7	12.7 (5.9-27.0)
	Eudravigilance: 5	9.7 (4.0-23.7)
Total	Lareb: 18	70.4 (41.9-118.3)
	WHO: 91	3.7 (3.0-4.6)
	Eudravigilance: 52	3.7 (2.8-4.9)

Mechanism

The peripheral ATEs may be predisposed due to the malignancy itself or due to the CBC. There are some theories how CBC could increase the risk. Obviously, endothelial damage seems to play a major role. Histological examination of the arterial blood vessel after cisplatin infusion showed damage characterized by intimal edema, thrombus formation and detachment of the intimal layer. Other hypotheses are elevation of von Willebrand factor, thromboxane-prostacyclin homeostatic disturbances and enhanced activity of monocytes in the blood [15,24,25]. An in-vitro study revealed that cisplatin up-regulates ICAM-1 in endothelial cells, an important protein to recruit circulating leukocytes to the blood vessel wall, as well [26]. Further found Sekijima *et al.* an increased significant arterial stiffness in patients with ovarian cancer or endometrial cancer treated with platinum based chemotherapy relative to patients which underwent only surgery [27]. Thereby might hypomagnesaemia caused by cisplatin be a possible risk, because it is associated with vasospasm [28].

The mechanism of malignancy related hypercoagulable state is complex, but several players have been identified [29]. Many solid tumor cell lines demonstrate increased expression of tissue factor, a

trigger of the extrinsic coagulation pathway. Another player is cancer procoagulant, a cysteine protease expressed by various tumor cell lines, which is able to activate factor X in the absence of factor VIIa. Malignancy related arterial clots are rare when compared with venous thromboembolism. Meanwhile an increased risk of cardiovascular events has been established in long term survivors of testicular cancer treated with BEP chemotherapy [30,31]. BEP chemotherapy had a 5.7 fold higher risk (95% CI, 1.9-17.1) for coronary artery disease compared with surgery [30]. It has also been showed that cisplatin is detectable in serum several years after administration and may continuously stimulate the endothelium [32]. Nuver *et al.* revealed increased plasma levels endothelial and inflammatory markers proteins (C-reactive protein, von Willebrand factor, plasminogen activator inhibitor and tissue-type plasminogen activator) after a median follow-up of seven years in survivors treated with CBC [31].
A possible mechanism is described but the whether the malignancy itself, cisplatin or a combination contributes to the risk of a (peripheral) ATE remains unclear. For now it seems that cisplatin on top of the pre-existing risk could increase the risk peripheral ATE.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb received 16 reports of peripheral ATEs associated with the use of CBC (3 monotherapy, 5 combined with pemetrexed, 5 combined with gemcitabine, 2 combined with bleomycin/etoposide and 1 combined with etoposide). In five reports amputation was necessary. Together with the most latency times described in literature, the peripheral ATEs seems to occur mainly shortly after the start with CBC. The association is supported by a possible pharmacological mechanism and a statistically significant disproportionality in the database of Lareb, the WHO and Eudravigilance. The association is well described in the literature by case reports and retrospective studies however more valid studies are lacking. Only one systematic review and meta-analysis showed thus far no increased risk of ATEs in patients treated with CBC. The 'confounding by indication' dilemma remains, but all the available cases received by Lareb, those described in literature and the possible severe consequences are worth noting for this signal. It could be that the patient's medical history and possible history of smoking has previously led to arterial disease and cisplatin has aggravated this. To recognize peripheral ATEs timely, knowledge and recognition of these complications are required. Further evaluation is needed to strengthen the possible increased risk of CBC and underlying risk factors.

- Peripheral arterial thromboembolic events or occlusion should be mentioned in all SmPCs of cisplatin.

References

1. SmPC Platosin©. (version date: 4-5-2011, access date: 1-9-2015) http://db.cbg-meb.nl/IB-teksten/h15255.pdf.
2. KNMP. Informatorium Medicamentorum. (version date: 2015, access date: 3-9-2015) https://kennisbank.knmp.nl/.
3. Seng S, Liu Z, Chiu SK, Proverbs-Singh T, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM, Oh WK, et al. Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol. 2012;30(35):4416-26.
4. SmPC cisplatin Teva. (version date: 11-6-2015, access date: 8-9-2015) http://db.cbg-meb.nl/IB-teksten/h11918.pdf.
5. SmPC cisplatin PCH. (version date: 16-3-2015, access date: 8-9-2015) http://db.cbg-meb.nl/IB-teksten/h101430.pdf.
6. Lareb Database. (version date: 2015, access date: 1-9-2015) http://databank.lareb.nl/Bijwerkingen?lang=nl.
7. Lareb Quarterly Report 2008-1: Cisplatin and cerebral infarction. (version date: 2008, access date: 31-8-2015) http://www.lareb.nl/Signalen/kwb_2008_1_cispla.
8. US SmPC cisplatin. (version date: 26-2-2015, access date: 3-9-2015) http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018057s083lbl.pdf.
9. SmPC generic cisplatin / Platosin®. (version date: 2015, access date: 3-9-2015) http://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:1:0:::RP,1:P0_DOMAIN,P0_LANG:H,NL.
10. SmPC cisplatin Mylan. (version date: 21-5-2015, access date: 8-9-2015) http://db.cbg-meb.nl/IB-teksten/h108358.pdf.
11. Mellema WW, van der Hoek D, Postmus PE, Smit EF. Retrospective evaluation of thromboembolic events in patients with non-small cell lung cancer treated with platinum-based chemotherapy. Lung Cancer 2014;86(1):73-7.

12. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, Soff G, Parameswaran R, Hassoun H. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29(25):3466-73.
13. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol. 2009;27(23):3786-93.
14. Doganci S, Kadan M, Kaya E, Erol G, Gunay C, Demirkilic U. Acute arterial thrombosis following chemotherapy in a patient with a gastric carcinoma. Cardiovasc.J Afr. 2013;24(2):e7-e9
15. Rishi A, Ghoshal S. Acute multiple arterial thrombosis after cisplatin in base of tongue carcinoma: case report. Head Neck. 2013;35(9):E269-E271
16. Cheng E, Berthold DR, Moore MJ, Duran I. Arterial thrombosis after cisplatin-based chemotherapy for metastatic germ cell tumors. Acta Oncol. 2009;48(3):475-7.
17. Mathews J, Goel R, Evans WK, Shamji F, Stewart DJ. Arterial occlusion in patients with peripheral vascular disease treated with platinum-based regimens for lung cancer. Cancer Chemother.Pharmacol 1997;40(1):19-22.
18. Numico G, Garrone O, Dongiovanni V, Silvestris N, Colantonio I, Di CG, Granetto C, Occelli M, Fea E, Heouaine A, et al. Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. Cancer 2005;103(5):994-9.
19. Weijl NI, Rutten MF, Zwinderman AH, Keizer HJ, Nooy MA, Rosendaal FR, Cleton FJ, Osanto S. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. J Clin Oncol. 2000;18(10):2169-78.
20. Proverbs-Singh T, Chiu SK, Liu Z, Seng S, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM, Oh WK, et al. Arterial thromboembolism in cancer patients treated with cisplatin: a systematic review and meta-analysis. J Natl.Cancer Inst. 2012;104(23):1837-40.
21. Yamashita T. Current status of hepatocellular carcinoma treatment in Japan: hepatic arterial infusion chemotherapy. Clin Drug Investig. 2012;32 Suppl 2:15-23.
22. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2015, access date: 1-9-2015) https://vigilyze.who-umc.org/?sSessionId=4B361961D8C2404B90D69D5DB95C2DE#/Search (Access restricted).
23. Eudravigilance database. (version date: 2015, access date: 7-9-2015) http://bi.eudra.org (Access restricted).
24. Nuver J, Smit AJ, van der Meer J, van den Berg MP, van der Graaf WT, Meinardi MT, Sleijfer DT, Hoekstra HJ, van Gessel AI, van Roon AM, et al. Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. J Clin Oncol. 2005;23(36):9130-7.
25. Dieckmann KP, Struss WJ, Budde U. Evidence for acute vascular toxicity of cisplatin-based chemotherapy in patients with germ cell tumour. Anticancer.Res. 2011;31(12):4501-5.
26. Yu M, Han J, Cui P, Dai M, Li H, Zhang J, Xiu R. Cisplatin up-regulates ICAM-1 expression in endothelial cell via a NF-kappaB dependent pathway. Cancer Sci. 2008;99(2):391-7.
27. Sekijima T, Tanabe A, Maruoka R, Fujishiro N, Yu S, Fujiwara S, Yuguchi H, Yamashita Y, Terai Y, Ohmichi M. Impact of platinum-based chemotherapy on the progression of atherosclerosis. Climacteric. 2011;14(1):31-40.
28. Altura BM, Altura BT, Carella A, Turlapaty PD. Hypomagnesemia and vasoconstriction: possible relationship to etiology of sudden death ischemic heart disease and hypertensive vascular diseases. Artery. 1981;9(3):212-31.
29. Park HJ, Ranganathan P. Neoplastic and paraneoplastic vasculitis, vasculopathy, and hypercoagulability. Rheum.Dis.Clin North Am 2011;37(4):593-606.
30. Haugnes HS, Wethal T, Aass N, Dahl O, Klepp O, Langberg CW, Wilsgaard T, Bremnes RM, Fossa SD. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol. 2010;28(30):4649-57.
31. Nuver J, Smit AJ, Sleijfer DT, van Gessel AI, van Roon AM, van der Meer J, van den Berg MP, Burgerhof JG, Hoekstra HJ, Sluiter WJ, et al. Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer. Eur J Cancer 2004;40(5):701-6.
32. Brouwers EE, Huitema AD, Beijnen JH, Schellens JH. Long-term platinum retention after treatment with cisplatin and oxaliplatin. BMC.Clin Pharmacol 2008;8:7

This signal has been raised on October 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB http://www.cbg-meb.nl/