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Severe vascular toxicity associated with vinblastine, bleomycin, and cisplatin chemotherapy*

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Summary. Vascular toxicity following the use of vinblastine, bleomycin, and cisplatin (VBP) combination chemotherapy has been described. This report gives details of 5 patients who suffered acute life-threatening vascular events following such a chemotherapy regimen for germ cell tumors. In 3 of the cases no evidence of tumor was found at autopsy. Both an acute and a long-term vascular toxicity were seen. Large artery vascular disease may result from synergistic toxicity of the drugs comprising the regimen. These cases, with an additional 16 collected from the literature, suggest that major vascular disease is a significant side-effect of the VBP regimen.

Introduction

Curative chemotherapeutic regimens exist for a diverse group of neoplasms. As treated patients survive longer, long-term complications of such regimens are becoming recognized. The combination of vinblastine, bleomycin, and cisplatin (VBP) dramatically changed the prognosis of advanced germ cell tumors [9], which now have a 70% 5-year survival [6]. The VAB-6 regimen (vinblastine, bleomycin, cisplatin, actionomycin D, and cyclophosphamide) is equally succesful [29]. Long-term complications of combination chemotherapy for germ cell tumors include renal dysfunction and hypomagnesemia [28], peripheral neuropathy, pulmonary dysfunction [4], skin hyperpigmentation [7], and acute nonlymphocytic leukemia [19].

Another significant side effect of the VBP regimen is Raynaud's phenomenon. This was initially associated with vinblastine and bleomycin [2, 24]. More complete characterization revealed that 37% of patients treated either with vinblastine and bleomycin or with VBP developed clinical Raynaud's phenomenon [27]. Smoking increases the frequency of this toxicity. Although bleomycin alone may cause Raynaud's phenomenon [14, 22], the combination of vinblastine and bleomycin is synergistic in producing this vasospastic phenomenon. Malignant hypertension related to marked thickening and hyperplasia of small renal arteries has been reported [11]. Increasing evidence indicates that disease of large arteries, including coronary [1, 5, 8, 10] and cerebral [3, 5, 15] vessels, may also result from VBP therapy.

We now report on a further five patients who died following therapy for germ cell carcinoma and in whom large artery vascular disease was causally related to their deaths.

Case reports

Of 65 patients with germ cell tumors seen at the University of Minnesota between 1978 and 1982 and treated with VBP, 4 suffered acute ischemic vascular events. A 5th patient was referred to the University of Chicago after being treated with VBP at another institution. The clinical data in the 5 cases is summarized in Table 1. The VBP chemotherapy regimen consisted of vinblastine 0.15 mg/kg on days 1 and 2, bleomycin 30 units on days 2, 9, and 16, and cisplatin 20 mg/m^2 on days 1 through 5, repeated every 3 weeks.

Patient 1. This 24-year-old white male presented to the University of Minnesota in November 1980 with a 3-month history of scrotal swelling. Orchiectomy at another hospital had revealed teratocarcinoma. A retroperitoneal lymph node disection revealed embryonal carcinoma involvement. Pulmonary nodules were noted, and chemotherapy with VBP was started. Complete remission was achieved after six cycles. He remained well for 18 months, and was then found dead in his dormitory room. He had no history of coronary artery disease and was a nonsmoker, but was grossly obese. The pretreatment ECG was normal. He did not receive mediastinal radiation. He was hypomagensemic for the duration of chemotherapy. At autopsy there was no evidence of tumor. There was 75% focal occlusion of the left anterior descending coronary artery, with a septal acute myocardial infarction, and 50% narrowing of the right coronary artery. The major arteries showed minimal atherosclerosis.

Patient 2. This 23-year-old white male presented with a mediastinal mass in September 1978. Thoracotomy and biopsy showed an endodermal sinus tumor. He had no testicular masses. He received four cycles of VBP, with some response. On day 16 of the fourth cycle he developed sudden rectal pain and bleeding. He died after a rapidly downhill course. *Clostridia* were cultured from blood cultures taken during resuscitation attempts. At autopsy, the mediastinal mass was necrotic, with no evidence of viable

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tumor. Rectal infarction was noted and was presumed to be the source of clostridial sepsis. No other major vascular lesions were noted.

Patient 3. This 42-year-old white male presented to another hospital in November 1977 with a large abdominal mass. Exploratory laparotomy revealed an anaplastic seminoma. Subsequent right orchiectomy showed seminoma. He received radiation therapy (35 Gy) to the abdomen (but not to the mediastinum), and low-dose cyclophosphamide, bleomycin, and doxorubicin. Since the retroperitoneal mass was still present he was referred to the University of Minnesota in March 1978. The abdominal mass was not detectable after three cycles of VBP chemotherapy. He had no history of coronary artery disease, but had a 25 pack-year smoking history. After a 46-month interval he presented in cardiogenic shock with renal failure and died shortly thereafter. At autopsy, an extensive acute myocardial infarction, involving the entire right ventricle, posterior interventricular septum, posterior and posterolateral left ventricle, and right atrial appendage was found. There was intimal thickening, fibrosis, and recent thrombosis of the right coronary artery. There was minimal atherosclerosis in the left anterior descending and circumflex coronary arteries. No viable tumor was found.

Patient 4. This 58-year-old white male presented in March 1978 with dyspnea, hemoptysis, and an enlarged submental lymph node. Biopsy of the node showed choriocarcinoma with embryonal elements. Evaluation revealed multiple pulmonary nodules. Chemotherapy with VBP was initiated. On day 6 of cycle 1 he developed acute left hemiparesis. Evalutaion, including computerized tomography, was negative. The hemiparesis slowly resolved. The patient received a further five cycles of VBP, after which he still had extensive pulmonary disease, and received cyclophosphamide, actinomycin D, and methotrexate. One month later, he developed worsening left hemiparesis and altered mentation. Computerized tomography was again normal. Cerebral angiography was consistent with occlusive arteritis in the right frontal and left temporoparietal regions. He died a few days later. No autopsy was performed.

Patient 5. This 33-year-old white male presented to another institution in November 1984 with dyspnea and weight loss and was found to have a left scrotal mass and multiple pulmonary nodules, as well as cervival and supraclavicular lymphadenopathy. Further evaluation showed retroperitoneal adenopathy and hepatic metastases. At orchiectomy, the tumor was found to be an embryonal carcinoma. Chemotherapy with VBP was started. He did not receive mediastinal irradiation. After four cycles he had persistent pulmonary and hepatic disease, and received VP-16 and cisplatin, without response. He was then referred to the Universtiy of Chicago, and received an investigational regimen (phase II) consisting of high-dose cytosine arabinoside. On day 15 of cycle 1 he was admitted to hospital with neutropenia, sepsis, and hypotension. Echocardiography showed marked right ventricular dilatation and dysfunction with minor left ventricular dysfunction. His ECG, initially normal, showed an evolving inferior infarction. A clinical diagnosis of right ventricular infarction was made although several other possiblities were also considered. The patient died 3 days after admission. No autopsy was performed.

Discussion

The increasing numer of reports of life-threatening and fatal vascular episodes following VBP therapy are of great concern. We have described five such cases in which the deaths of the patients were solely or partially due to an acute vascular event. Several reports documenting major vascular disease following this therapy are summarized in Table 2.

There may be both an acute and a long term vascular toxicity. In Kukla's four cases of cerebrovascular accident [19] and in our patient 4, symptoms developed within 48 h of the first treatment. Severe angina and acute myocardial infarction have been noted soon after vincristine [23] or

Table 1. Patient characteristics

Age (years)	Histology	Therapy	Outcome of therapy	Vascular event	Outcome
24	Teratocarcinoma embryonal ca.	VBP	CR	Acute myocardial infarction	Died
23	Endodermal sinus	VBP	CR	Rectal infarction	Died
42	Seminoma	VBP	CR	Acute myocardial infarction	Died
58	Choriocarcinoma + embryonal Ca	VBP	NR	Cerebrovascular accident	Died
33	Embryonal Ca	VBP	NR	Acute myocardial infarction	Died

VBP, vinblastine, bleomycin, and cisplatin; CR, complete response; NR, no response

Table 2. Vascular events reported in the literature

Authors [ref.]	No. of patients	Chemotherapy regimen(s)	Vascular events	Outcome of events
Edwards et al. [8]	2	VBP	Coronary artery disease	2 Dead
Bodensteiner [1]	1	VBP	Myocardial infarction	1 Dead
Greist et al. [10]	6	VBP	Coronary artery disease	3 Alive
		VBP + doxorubicin		3 Dead
Kukla et al. [15]	4	Vincristine + BP	Cerebrovascular accident	4 Dead
Cohen et al. [3]	1	VBP	Transient hemianopsia (? neurotoxicity)	1 Alive

V, vinblastine; B, bleomycin; P, cisplatin

vinblastine [16] therapy. One patient, reported by Bodensteiner et al., suffered a clinically documented acute myocardial infarction after the first cycle of therapy, and a fatal myocardial infarction 7 month later, without further chemotherapy. At autopsy, coronary artery fibrosis was found [1]. In initial toxicity studies, bleomycin was found to cause acute necrotizing coronary arteritis in rhesus monkeys [20], but the long-term potential of this lesion to result in arterial fibrosis was not assessed. Severe hypomagnesemia causes ventricular fibrillation [12], and therefore cisplatin-induced hypomagensemia could contribute to early cardiovascular morbidity. How acute vascular toxicity is related to more long-term vascular morbidity is not yet clear.

Raynaud's phenomenon becomes clinically evident a mean of 10 months after the start of therapy [27]. Coronary artery disease may occur months to years after therapy. The cause of this chronic vascular toxicity is obscure, and the relative contributions of various drugs is unknown. Autonomic neuropathy induced by vinblastine and microvascular changes seen after bleomycin are clearly long term in nature. Hypomagnesemia occurs in 87% of testicular cancer patients treated with cisplatin [28] and may persist for up to 3 years [21]. Since, under hypomagnesemic conditions, arterial smooth muscel showes increased sensitivity to agents which induce contraction [25], cisplatin may also contribute to long-term vascular toxicity.

A high level of circulating von Willebrand's factor antigen has been associated with Raynaud's phenomenon, and is thought to be a marker of endothelial injury [13]. Increased levels of this antigen were reported in patients who subsequently suffered cerebrovascular accidents following cisplatin-containing chemotherapy [17]. In addition, qualitative abnormalities of the von Willebrand factor molecule have been associated with thrombosis following therapy for acute lymphoblastic leukemia [18].

On the basis of our experience with these five patients and two previously reported [26] and of a careful review of the literature, we suggest that the combination of vinblastine, bleomycin, and cisplatin as used in the therapy of germ cell tumors is associated with life-threatening vascular toxicities. Although there is as yet no direct evidence linking VBP chemotherapy to these vascular events, we believe that the circumstantial evidence is strong. The vascular toxicity of chemotherapeutic agents, including that of cisplatin-based therapy for germ cell tumors, has been the subject of a recent review [5]. The potential toxicity is serious, and might not ordinarily be watched for, since the age group at risk for germ cell tumors normally has a low prevalence of major vascular disease. This is particularly significant because these young patients have an excellent outlook for cure of their malignancies. We believe that it is therefore important that the possibility of an acute vascular event, either at time of therapy or months to years later, be brought to the attention of physicians treating such patients. Prospective monitoring of von Willebrand factor antigen levels may be a means of predicting potential vascular toxicity. It is also important to continue the search for regimens which are equally efficacious, but which have less long-term toxicity in the treatment of testicular carcinoma.

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