would most likely be with chemotherapy whilst pregnant and depending on her response would receive involved field radiotherapy. Radiation induced malignancy, as a pathological entity may be seen more frequently due to improved survival of cancer patients resulting from an increased effectiveness of cancer therapy. The prognosis of radiation induced malignancies is in general is poor and the treatment options are limited, therefore early diagnosis and active lifelong surveillance may lead to a correspondingly better chance of salvage therapy. However, one has to emphasize that the incidence of radiation-induced malignancies is small and that the risk of its occurrence is vastly outweighed by the benefits obtained from radiation therapy by most patients.

References

[1] Cahan WG, Woodard HQ, Higginbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone: Report of eleven cases 1948. Cancer 1998;82:8–34.
[2] Amemiya K, Shibuya K, Yoshimura R, Okada N. The risk of radiation-induced cancer in patients with squamous cell carcinoma of the head and neck and its results of treatment. Br J Radiol 2005;78:1028–33.
[3] O'Connor TA, McLean P, Juillard GJF, Parker RG. Olfactory neuroblastoma. Cancer 1989;63:2426–8.
[4] Skarsgard DP, Groome PA, Mackillop WJ, Zhou S, Rothwell D, Dixon PF, et al. Cancers of the upper aerodigestive tract in Ontario, Canada and the United States. Cancer 2000;88:1728–38.
[5] Berger L, Luc G, Richard D. L'esthésioneuroépithéliome olfactif. Bull Assoc Franç Étude Cancer 1924;13:410–21.
[6] Mark RJ, Poen J, Tran LM, Fu YS, Selch MT, Parker RG. Postirradiation sarcomas. A single-institution study and review of the literature. Cancer 1994;73:2653–62.
[7] Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Eng J Med 1993;328:1002–6.
[8] Murray EM, Werner D, Greeff EA, Taylor DA. Postradiation sarcomas: 20 cases and literature review. Int J Rad Oncol Biol Phys 1999;45:951–61.
[9] Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. Arch Surg 1992;127:1379–85.
[10] Hyams VJ. Olfactory neuroblastoma. In: Hyams VJ, Baksakis JG, Michaels L, editors. Tumours of the upper respiratory tract and ear. Washington DC: Armed Forces Institute of Pathology; 1988. p. 516–31.

Acute ischemia of the lower limb during chemotherapy for testicular cancer: A report of two cases

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To the Editor

Arterial or venous thrombosis is a common complication in cancer patients, particularly during treatment. This is especially true with some anti-angiogenic drugs (bevacuzimab, thalidomide) which are know to favor arterial thrombosis. Arterial complications are also described with chemotherapy regimens using cisplatin (CDDP) alone, particularly for testicular cancer. We report two cases of acute ischemia of the lower limb observed in patients given a CDDP based regimen for testicular cancer.

The first patient was a 36-year-old man with an uneventful personal and familial history, excepting active smoking evaluated at 20 package-years, who consulted for discomfort in the right testicle. Clinical work-up and computed tomography (CT) revealed a tumor of the right testis and lymph node enlargement of the mediastinal and aorta-cava chains. Tumor markers were negative. Right orchidectomy was performed via an inguinal approach and pathology examination of the surgical specimen disclosed exclusive seminoma, staged pT1N2M0 (no vascular

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emboli). A 4-cycle chemotherapy regimen (etoposide 100 mg/m^2/d for 5 days + cisplatin 20 mg/m^2/d for 5 days) was started.

Three days after the end of the first cycle, i.e. eight days after initiating the first cycle, the patient complained of pain in the left calf. Physical examination showed a pale left foot, a swollen calf, and sensorial deficit, leading to the diagnosis of arterial thrombosis. Emergency embolectomy with a Fogarty catheter was performed to clear the left femoropopliteal-tibial arterial vasculature. Continuous heparin infusion was then given and followed by low-molecular-weight heparin (LMWH). Nine days later, the patient developed recurrent thrombosis of the same arterial territory, requiring a second embolectomy and aponeurotomy. The patient recovered well under anticoagulants. Pathology (both events) reported a fibrin clot with no sign of malignancy. Echocardiography was normal.

The three other chemotherapy cycles were delivered successfully with no vascular events. At the end of the treatment schedule, the patient had achieved complete remission.

The second patient was a 34-year-old smoker (10–15 package-years) with a history of urological surgery (cure for a right ectopic testis and bilateral orchidopexia for torsion of the right testicle) who consulted for increased volume and pain in the left testicle. Clinically, the patient presented a mass in the left testicle. Left orchidectomy was performed via the inguinal approach. Pathology reported a 7-cm mixed predominantly seminomatous germinal tumor with an embryonic carcinoma component. The cord was negative and there were no vascular emboli. Search for extension identified two enlarged left retroperitoneal lateral aortic nodes measuring 20 mm. Staging was pT1N1M0. A three-cycle chemotherapy protocol was planned: BEP (Etoposide 100 mg/m^2/d for 5 days + Cisplatin 20 mg/m^2/d for 5 days, Bleomycin 30 mg/d d1, d8 and d15). On day 15 counting from onset of the first cycle, the patient complained of sudden painful cramps in the left calf. Walking distance was limited to 150 m with no sensorial or motor deficit. The arterial pulses were palpated and free of bruit, excepting the posterior tibial. A duplex Doppler of the venous and arterial networks of the lower limb performed two days later disclosed thrombosis of the left middle popliteal artery with a recent obstructive thrombus and thrombosis of the peroneal artery which had only been reinjected in the lower third of the leg. A Fogarty catheter was used to clear the lower popliteal and tibial networks. Pathology reported fibrin clots with no sign of malignancy. Heparin was delivered intravenously in a continuous infusion then replaced with oral anticoagulants. Anticoagulation was difficult to control during chemotherapy. A control duplex-Doppler two weeks later revealed good patency of the lower limb arterial network. At last follow-up the patient has remained in complete remission.

Discussion

We report two similar cases of acute lower limb ischemia in two young male smokers with germ-cell tumors (seminoma in one patient and a mixed tumor in the other). The two patients were given similar chemotherapy regiments (4 EP, 3 BEP) and both developed arterial thrombosis during the first cycle.

Three pathogenic mechanisms could be put forward to explain the development of arterial thrombosis in these patients: drug toxicity, cancer of the testicle, smoking.

In both patients, the arterial thrombosis occurred early after initiation of the first chemotherapy cycle, a chronological argument in favor of drug toxicity in young patients with no radiological evidence of artherosclerosis [1]. Chemotherapy-related vascular phenomenon are well known, e.g. Raynaud's phenomenon, which some authors believe has a reduced incidence because of concomitant use of corticosteroids, and arterial thrombosis [2–4]. Drug-induced thrombosis appears to be related to damage to the vascular endothelium, platelet activation, and alteration of the coagulation cascade. Bleomycin can cause venous obstruction, changes in the capillary and arteriole endothelium and *in vitro* stimulates production of collagen in fibroblast cultures. Cisplatin might also be incriminated [5–7] and in some instances the thrombosis could hit the aorta [8]. Several factors could be associated: smoking (both patients were active smokers), renal toxicity of cisplatin (not observed here), increased Willebrand factor, and severe hypomagnesemia leading to arterial vasospasm often reported in older studies [9] and due to cisplatin-induced tubulopathy (serum magnesium was not assayed in these patients).

A second hypothesis would be cancer-induced thrombosis. Thromboembolism is common in cancer patients, but arterial thrombosis is rarely described. However, in a recent meta-analysis comparing the risk of arterial thromboembolism in 1745 patients with metastatic colorectal, breast or non-small-cell cancer given chemotherapy regimens with and without associated bevacizumab [10], the risk was 3.1 events per 100 patient-years among patients receiving chemotherapy alone and 5.5 for those receiving a combination with bevacizumab. In another cohort study [11] reviewing first-line treatment in 179 patients with testicular cancer between 1979 and 1997, from treatment onset to six weeks after

treatment end, 15 patients experienced 18 thrombotic events, including three arterial events. There would thus be no reason to postulate a higher risk specifically among patients with testicular cancer, excepting the fact that the baseline risk would be expected to be very low in this younger population. This study found that risk factors for thrombosis were the presence of liver metastasis and high-dose corticosteroids ($>$80 mg dexamethasone). Neither of our patients had liver metastases, but both received more than 420 mg prednisolone (the dose equivalent of 80 mg dexamethasone). Corticosteroids can induce thrombosis via a vasoconstrictor effect and a coagulation effect. At high doses, corticosteroids inhibit fibrinolytic activity while at low doses, they inhibit platelet aggregation, and consequently, affecting the risk of arterial thrombosis.

The third hypothesis of a smoking effect must also be considered, perhaps more as a co-factor than as a unique causal element.

Thus, cases of arterial thrombosis of the lower limb in patients given chemotherapy for testicular cancer are not exceptional, particularly when high-dose corticosteroids are given to counteract the emetic effect of chemotherapy regimens using cisplatin. While it would probably be hazardous to propose preventive anticoagulation systematically, clinicians must not overlook the possibility of arterial thrombosis, even in this young population. As for venous thrombosis, and particularly in the field of pancreatic cancers [12], the debate remains open concerning the continued use of LMWH for the curative treatment of arterial thrombosis in cancer patients [13].

References

[1] Nichols CR, Roth BJ, Williams SD, Gill I, Muggia FM, Stablein DM, et al. No evidence of acute cardiovascular complications of chemotherapy for testicular cancer: An analysis of the Testicular Cancer Intergroup Study. J Clin Oncol 1992;10:760–5.

[2] Doehn C, Büttner H, Fornara P, Jocham D. Fatal basilar artery thrombosis after chemotherapy for testicular cancer. Urol Int 2000;65:43–5.

[3] Lepidini G, Biancari F, D'Andrea V. Severe thrombosis after chemotherapy for metastatic choriocarcinoma of the testis maintaining complete remission for a long period. Scand J Urol Nephrol 1997;31:221–2.

[4] Schmidt J, Zenut M, De Marquilly F, Maciejewski C, Plagne R, Lavarenne J. Arterial thrombosis in a patient after chemotherapy (BEP protocol) for extra-gonadal dysgerminoma. Thérapie 1995;50:476–8.

[5] Içli F, Karaoguz H, Dinçol D, Demirkazik A, Günel N, Karaoguz R, et al. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer 1993;72:587–93.

[6] Illaramendi JJ, Gallego J. Cisplatin-based chemotherapy and acute cerebrovascular events. Lancet 1991;338:705.

[7] Cheng E, Berthold DR, Moore MJ, Duran I. Arterial thrombosis after cisplatin-based chemotherapy for metastatic germ cell tumors. Acta Oncol 2008 (in press).

[8] Grenader T, Shavit L, Ospovat I, Gutfeld O, Peretz T. Aortic occlusion in patients treated with Cisplatin-based chemotherapy. Mt Sinai J Med 2006;73:810–2.

[9] Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, renal dysfunction, and Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. Cancer 1985;56:2765–70.

[10] Scappaticci FA, Shillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232–9.

[11] Weijl NI, Ruten MF, Zwinderman H, Keizer HJ, Nooy MA, Rosendaal FR, et al. Thromboembolic events during chemotherapy for germ cell cancer: A cohort study and review of the literature. J Clin Oncol 2000;18:2169–78.

[12] Sgouros J, Maraveyas A. Excess premature (3-months) mortality in advanced pancreatic cancer could be related to fatal vascular thromoboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer. Acta Oncol 2008;47:337–46.

[13] Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–53.