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Pemetrexed and Carboplatin are two well-known chemioterapic agents used for the treatment of many tumors, especially for lung cancer and mesothelioma. Peripheral ischemic events related to Pemetrexed and Carboplatin are rarely reported.

We herein report a case of lower limb acute ischemia related to combined treatment of Pemetrexed and Carboplatin. A 68-year-old woman was given the chemiotherapeutic treatment with combination of Pemetrexed and Carboplatin after pleural resection for a malignant pleural mesothelioma. Immediately after the second cycle of treatment, the patient experienced sudden acute left lower limb ischemia. Symptoms resolved after an intra-operative thrombolytic and spasmolytic therapy.

KEY WORDS: Acute ischemia, Chemotherapy, Endovascular treatment, Malignant Pleural Mesothelioma

Introduction

Arterial or venous thrombosis events are not so rare in cancer patients, especially during treatment. This is particularly well known with some antiangiogenic drugs (i.e. thalidomide, bevacizumab) that can cause arterial thrombosis. Arterial complications are also described with chemotherapy using cisplatin. Recently, a German survey documented an incidence rate of 0.3% of serious

arterial cardiovascular events occurring during the time of chemotherapy with this drug ¹. On the contrary, the combination of pemetrexed and carboplatin has exhibited significant antitumor activity, with mild manageable toxicity in patients with advanced cancer ². We herein report a case of lower limb ischemia in a lady submitted to two cycles of combined chemotherapy with pemetrexed and carboplatin for malignant pleural mesothelioma (MPM).

Case report

A 68-year-old woman was referred urgently to our institution for acute left lower limb ischemia with coldness and mottling of the foot (pallor, purplish and cyanotic areas) (Fig. 1), motor function was impaired, but sensor function was not affected. Her clinical history was remarkable for celiac disease and arterial hypertension. She denied any history of thrombotic

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Fig. 1: Picture of the left foot at the time of admission showing mottling of the skin in plantar region.

events. One year before she was submitted to pleural resection for a stage II disease according to the International Mesothelioma Interest Group³ staging system and a combination of pemetrexed (500 mg/m²) and carboplatin (AUC5) chemotherapy was then started. At admission, one day after the completion of the second cycle, peripheral arterial pulses were not present and a Duplex scan of the lower limbs showed an acute occlusion of the left tibio-peroneal trunk with no flow in the ipsilateral below-the-knee vessels. An urgent arteriography was carried out through a contralateral right femoral access confirming the Duplex scan findings and highlighting the presence of several spasms along the tibial vessels course (Fig. 2). We discussed the situation and decided to perform an endovascular approach using loco-regional transcatheter thrombolysis with urokinase to prevent subsequent tissue necrosis, avoiding large surgical incisions and arterial trauma. After placement of 5fr multiholes multipurpose catheter in the left popliteal artery, a 200.000 IU bolus was administered. The treatment was continued with infusion of 70.000 I.U. of urokinase/hour and 100 mg of lidocaine for 24 hours combined with intravenous administration of heparin (15.000 I.U. for 24 hours), according to our standard protocol⁴. The application of

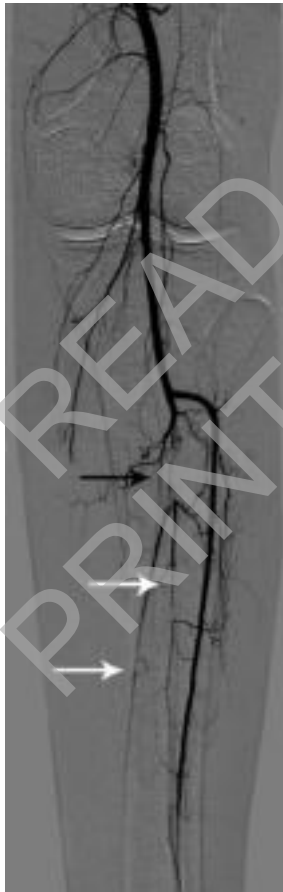


Fig.2: Overview angiography showing tibio-peroneal trunk occlusion (black arrow) and spasms of posterior tibial artery and peroneal artery (white arrows).



Fig.3: Control angiography after 24 hours demonstrating patent vessels below-the-knee vessels with residual thrombus in the tibio-peroneal trunk.



Fig.4: Complete angiogram showing complete resolution of the occlusion and spasms

heparin for anticoagulation (PTT 60-80 s) is required to maintain patent collaterals and inhibit further expansion of possible thrombus. After this treatment, control angiogram showed partial recanalization of the tibio-peroneal trunk with resolution of arterial spasms (Fig. 3) thus another 24-hours of thrombolytic and spasmolytic therapy was continued. The last angiogram demonstrated the complete recanalization of the tibio-peroneal trunk with good run-off in the anterior tibial artery down to the foot (Fig. 4). The following day she underwent a control Duplex-scan showing direct flow to the foot. She was discharged on post-operative day 3 on anti-platelet therapy (clopidogrel 75 mg a day). Follow-up Duplex scan after three months demonstrated good flow in the tibial vessels without clinical signs of recurrent limb ischemia. Unfortunately, due to the aggressiveness of the tumor, her prognosis was very poor and she died 6 months after this treatment.

Discussion

MPM is the most common type of mesothelioma with a reported incidence of 1.4/100.000 for men and

0.3/100.000 for women. Peak incidence occurs between 70-74 years for both sexes⁵. To date, multimodality approach combining surgery, radiotherapy and chemotherapy is considered the most effective treatment strategy⁶. The most effective agents are antimetabolites, platinum and anthracyclines but with poor results in terms of local recurrence control and survival rates and with important toxicity. Pemetrexed, a multifolate antagonist blocking three metabolic pathways of folate metabolism, in some series is used in single modality therapy showing better outcomes in comparison with other single agents⁷. Pemetrexed has demonstrated clinical activity in non-small-cell lung cancer, as well as in a wide array of other solid tumors, including mesothelioma, breast, colorectal, bladder, cervical, gastric and pancreatic cancer. Combined modality treatment with cisplatin, carboplatin and gemcitabine has been proven feasible and shows encouraging activity in lung cancer and MPM. For MPM patients the gold standard chemotherapy is the combination of pemetrexed plus cisplatin but also the combination of pemetrexed plus carboplatin is feasible and more tolerated⁸⁻¹⁰. Our 68-years-old female patient had already done two cycles of chemotherapy in combination with pemetrexed plus carboplatin and she was planning to start for the third cycle. She denied any history of thrombotic events and she never presented either peripheral vascular disease or plaque formation. Her echocardiographic examination indexed upon normal limits.

To the best of our knowledge, this is the first report describing pemetrexed – carboplatin combination induced lower limb ischemia. In the literature, there is only one case, which describes the association of MPM with arterial ischemia. In this paper a 54-year-old gentleman experienced an acute stroke caused by carotid occlusion probably due to a para-neoplastic syndrome¹¹; an emergency open surgical repair via carotid thrombectomy was effective to treat that patient. In our case, we decided to proceed to a minimal invasive approach with a loco-regional transcatheter thrombolysis with urokinase and spasmolysis using lidocaine under local anesthesia avoiding general and epidural anesthesia, not desirable in such critical patient. To prevent an early re-occlusion of the artery after the thrombolytic treatment, intravenous heparin therapy was continued for 4 days, until a sustained result was obtained. Different medications have been used for thrombolysis, such as urokinase, r-tPA, streptokinase; we used urokinase since no drug was described to be better than others^{12,13}.

The right therapeutic strategy is not yet defined and depends on the symptoms and clinical findings. Intra-arterial therapy may be indicated in early stages with ischemia but without tissue necrosis. As a result of the combination of acute thrombosis and spasm, probably combined local thrombolysis, anticoagulation and spasmolysis could be successful to save the leg.

Conclusions

The present case highlights the potential risk for the development of acute limb ischemia following pemetrexed-based chemotherapy. Future studies should be conducted to explain the mechanisms through which these drugs may eventually cause acute ischemic events.

Riassunto

Il Pemetrexed ed il carboplatino sono farmaci chemioterapici di uso corrente nel trattamento di molti tumori, in particolar modo del cancro del polmone e del mesothelioma pleurico. In letteratura sono raramente riportate complicanze ischemiche periferiche relative all'uso del pemetrexed e del carboplatino.

Scopo di questo lavoro è descrivere un caso di ischemia acuta d'arto dopo trattamento con pemetrexed e carboplatino. Una donna di 68 anni fu sottoposta a ciclo chemioterapico con pemetrexed e carboplatino dopo decorticazione pleurica per un mesothelioma pleurico maligno. Alla conclusione del secondo ciclo di trattamento, la paziente sviluppò improvvisa ischemia acuta all'arto inferiore sinistro. Trasportata d'urgenza presso il nostro Istituto, fu sottoposta ad esame arteriografico e successivo trattamento trombolitico e spasmolitico trans-catetere che portarono alla completa risoluzione del quadro clinico.

References

1. Dieckmann KP, Gerl A, Witt J, Hartmann JT: *Myocardial infarction and other major vascular events during chemotherapy for testicular cancer*. Ann Oncol, 2010; 21:1607-11.
2. Grønberg BH, Bremnes RM, Fløtten O, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stormes F, Tollåli T, Wammer F, Aasebø U, Sundstrøm S.: *Phase III study by the Norwegian lung cancer study group: Pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer*. J Clin Oncol, 2009; 27:3217-24.
3. Rusch VW: *A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group*. Chest, 1995; 108:1122-128.
4. Porcellini M, Cecere D, Carbone F, Bracale UM, Di Lella D, Russo A, del Guercio L, Bracale GC: *Thrombolysis and endovascular procedures for the treatment of infrainguinal chronic arterial occlusions*. J Vasc Endovasc Surg, 2004; 11:65-71.
5. Budroni M, Cossu A, Paliogiannis P, Palmieri G, Attene F, Cesaraccio R, Tanda F: *Epidemiology of malignant pleural mesothelioma in the province of Sassari (Sardinia, Italy) A population-based report*. Ann Ital Chir, 2013, 28; 84. pii: S0003469X13021192.
6. Pala C, Paliogiannis P, Serventi F, Trignano E, Trignano M: *Multimodality approach to malignant pleural mesothelioma. A case report*. Ann Ital Chir, 2010; 81:37-40.
7. Adjei AA: *Pemetrexed (ALIMTA), a novel multitargeted antineoplastic agent*. Clin Cancer Res, 2004; 10:4276s-4280s.
8. Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, Serra M, Muzio A, Carbone R, Buosi R, Galbusera V, Piccolini E, Giaretto L, Rebella L, Mencoboni M: *Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM)*. Ann Oncol, 2008; 19:370-73.
9. Pasello G, Altavilla G, Bonanno L, Rea F, Favaretto AG: *A pathological complete response after preoperative chemotherapy with carboplatin and pemetrexed in malignant pleural mesothelioma: A case report*. Oncologist, 2013; 18:1118-25.
10. Ceresoli GL, Zucali PA, Favaretto AG, Grossi F, Bidoli P, Del Conte G, Ceribelli A, Bearz A, Morengi E, Cavina R, Marangolo M, Parra HJ, Santoro A: *Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma*. J Clin Oncol, 2006; 24:1443-448.
11. Ferrero E, Ferri M, Viazzo A, Gaggiano A, Berardi G, Piazza S, Cumbo P, Nessi F: *Mesothelioma and internal carotid artery occlusion: acute ischemic stroke and efficacy of emergency carotid thrombectomy*. Ann Vasc Surg, 2010; 24:257.e9-12.
12. Andreev A, Kavrakov T, Petkov D, Penkov P: *Severe acute hand ischemia following an accidental intraarterial drug injection, successfully treated with thrombolysis and intraarterial Iloprost infusion. Case report*. Angiology, 1995; 46(10):963-67.
13. Turba UC, Bozlar U, Simsek S: *Catheter-directed thrombolysis of acute lower extremity arterial thrombosis in a patient with heparin-induced thrombocytopenia*. Catheter Cardiovasc Interv, 2007; 70:1046-50.