DÜZCE TIP FAKÜLTESİ DERGİSİ
DUZCE MEDICAL JOURNAL
OLGU SUNUMU / CASE REPORT

ACUTE ARTERIAL THROMBOSIS FOLLOWING CAPECITABINE, CISPLATIN, TRASTUZUMAB COMBINATION IN METASTATIC GASTRIC ADENOCARCINOMA

Metastatik Mide Kanserinde Kapesitabin, Sisplatin, Trastuzumab Kombinasyonunu Takiben Gelişen Akut Arteryal Trombozis

[1] Berna BOZKURT DUMAN

[1] Adana Numune Training and Research Hospital.

ÖZET

Kanser hastalarında tromboz çok sayıda nedene bağlı olarak gelişebilmektedir. Kanser hastalarında tromboz genel populasyona göre çok daha fazladır. Kemoterapi ilişkili arteryal tromoz çok nadiren rapor edilmiştir. Kanser hastalığı hiperkoagulibiteye neden olan bir durumdur. Sisplatin bu yan etkiden en çok sorumlu tutulan ajandır. Sisplatinin bu vaskuler olayı nasıl tetiklediği bilinmemektedir. Endotelyal hasarlanma temel rol oynayan faktör olarak gözlenmektedir. Diğer sorumlu tutulan hipotezler plazmada sisplatinin indüklediği von Willebrand faktör yüksekliği, pıhtılaşma kaskadının aktivasyonu, tromboksan prostosiklin homostatik bozukluğu ve fibroblast stimulasyonudur. Bu vaka dolayısıyla kapesitabin, sisplatin, trastuzumab kombinasyonunun nadir yan etkisi sunulmuştur.

Anahtar kelimeler: capecitabine, cisplatin, trastuzumab, arteryal trombozis

ABSTRACT

The increased risk of thrombosis in patients with active cancer has multiple causes. Although venous thrombosis is more common in patients with cancer than in the general population, chemotherapy-induced arterial thrombosis rarely has been reported. Patients with cancer are in a hypercoagulable state. Cisplatin seems the most responsible from this adverse event. The mechanism by which cisplatin triggers vascular events is unknown, but endothelial damage seems to play a major role. Other proposed hypotheses are cisplatin-induced elevation of plasma levels of von Willebrand factor, alteration of clotting cascade, thrombaxane–prostacyclin homeostatic disturbances, and stimulation of fibroblasts(1-3). Here we report a rare side effect that became after capecitabine, cisplatin, trastuzumab combination.

Key words: capecitabine, cisplatin, trastuzumab, arterial thrombosis

Submitted/Başvuru tarihi:
30 06 2013
Accepted/Kabul tarihi:
10 04 2016
Registration/Kayıt no:
13 06 308

Corresponding Address / Yazışma Adresi:

Dr.Berna BOZKURT DUMAN

Adana Numune Training and Research Hospital

E-mail: berboz@hotmail.com

CASE REPORT

Fifty-seven years old female patient was admitted to the hospital because of abdominal pain that lasting for 3 months. After total abdominal and throcal body computed tomography, she was referred to our hospital for further management. Panendoscopy was performed because of mass that was detected at the total abdominal computed tomography. Histopathological examination was consistent with adenocarcinoma of the stomach. Positron emission tomography (PET-CT) was performed before chemotherapy was administered. Multiple lung and liver metastasis were detected.The Eastern Cooperative Oncology Group (ECOG) performance status was zero. Baseline left ventricular ejection fraction (LVEF) was normal HER2 3(+++) with immunohistochemistry and FISH was positive (HER2:CEP17 ratio ≥2). Chemotherapy was given every 3 weeks. Capecitabine 1000 mg/m2 was given orally twice a day for 14 days followed by a 1-week rest. Cisplatin 80 mg/m2 on day 1 was given by intravenous infusion. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks . First cycle was given. Treatment was well tolareted by patient but after 11 days from first cycle's first day acute arterial trombosis on left arm was detected when capecitabine ongoing at Doppler USG.. Arterial angiography was performed. Patient had newly diagnosis of Diabetes mellitus(DM) there was no comorbid disease(except DM) and there was no trombosis history .

Urgent thromboembolectomy was performed by cardiovasculer surgeon. it occurred again after 4-5 days and she operated again. Low moleculer weight heparin was given to the patient. Patient's arm was normal LMWH was given to the patients. The Naranjo Adverse Drug Reactions Probability Scale (NADRPS) was assessed. The score was 7. Adverse drug reaction category was probable for NADRPS.

Second cyle was given with Cisplatin dose reduction in the rate of 25% and capecitabine and trastuzumab were given same dose with LMWH. There was no problem after second and third cycle. Patient were at follow up. Response assessement was planned.

e-ISSN 1307- 671X
www.tipdergi.duzce.edu.tr
duzcetipdergisi@duzce.edu.tr

DISCUSSION

The increased risk of thrombosis in patients with active cancer has multiple causes. Although venous thrombosis is more common in patients with cancer than in the general population, chemotherapy-induced arterial thrombosis has been rarely reported. Patients with cancer are in a hypercoagulable state (2).

The thrombotic events may be predisposed due to cancer itself or due to the effect of chemotherapeutic agents. Cisplatin is known to increase the risk of thromboembolic events and is the agent most commonly implicated in patients with cancer and arterial thrombosis (2).

In fact, most cases of cisplatin-induced arterial thrombosis described in the literature occurred in patients with at least one of the foregoing risk factors (2). In a recent retrospective analysis by Moore and colleagues, data from 932 patients treated with cisplatin-based chemotherapy was analyzed; of these, 18% experienced thromboembolic events, mainly venous thromboembolism. Less than 2% experienced arterial thrombosis (3).

There was no report about arterial trombosis with capecitabine and trastuzumab. Rates of cardiac adverse events did not differ between groups the trastuzumab plus chemotherapy versus chemotherapy alone (17 [6%] vs 18 [6%]) in ToGA trial. Frequency

Rates of grade 3 or 4 cardiac adverse events did not differ between groups in this trial. Four (1%) patients in the trastuzumab plus chemotherapy group had a total of five events (cardiac

failure [two events in one patient], myocardial infarction, unstable angina, and myocardial ischaemia with tachycardia) compared with nine (3%) patients in the chemotherapy alone group, who had nine events (cardiac failure [two events], myocardial infarction [two events],

coronary arteriospasm, atrial fl utter, cardiac arrest, cardiorespiratory arrest, and Prinzmetal angina) in ToGA trial. Adverse events were generally mild; the most common grade 3/4 events were neutropenia, anemia, anorexia, and nausea. There was no thromboembolic event was reported in ToGA trial (1).

In one systematic review a total of 8216 patients from 38 trials were included. Among patients treated with cisplatin-based chemotherapy, the summary incidence of ATEs was 0.67% (95% CI = 0.40% to 0.95%), and the RR of arterial thromboembolism(ATE) was 1.36 (95% CI = 0.86 to 2.17; P = .19). No increase in ATEs was detected in any prespecified subgroup in this rewiev (4).

In this patient; Cisplatin seems the most responsible agent from this adverse event. The mechanism by which cisplatin triggers vascular events is unknown, but endothelial damage seems to play a major role. Other proposed hypotheses are cisplatin-induced elevation

of plasma levels of vWF, alteration of clotting cascade, thrombaxane–prostacyclin homeostatic disturbances, and stimulation of fibroblasts(2). Our patient's vWF level was higher; this result supports the hypothesis about cisplatin –induced thromboembolism. But it is not exact the other agents should have additive effect. But the strong problem is management of this patient. The randomized PROTECT (Prophylaxis of Thromboembolism during Chemotherapy) trial have shown benefit of primary prevention from thromboembolism with cisplatin-based combination chemotherapy in metastatic gastrointestinal or testicular cancers (5). This regimen should be given with primary prevention with LMWH, especially in patients who have high risk factors for thromboembolism.

REFERENCES

1-Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97. Epub 2010 Aug 19.

2-Rishi A, Ghoshal S. Acute multiple arterial thrombosis after cisplatin in base of tongue carcinoma: Case report. Head Neck. 2012 Aug 23. doi: 10.1002/hed.23123.

3- 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 Sep 1;29(25):3466-73.

4-Proverbs-Singh T, Chiu SK, Liu Z, Seng S, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM, Oh WK, Galsky MD. Arterial thromboembolism in cancer patients treated with cisplatin: a systematic review and meta-analysis. J Natl Cancer Inst. 2012 Dec 5;104(23):1837-40. doi: 10.1093/jnci/djs435. Epub 2012 Oct 23. Review.

5- Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009;10:943–949.