Journal of BUON **16:** 372-377, 2011

LETTERS TO THE EDITOR

Clinical and pathological characteristics of very young breast cancer patients (≤ 25 years of age)

Dear Editor,

Breast cancer occurs rarely in young women. Age less than 35 years is an independent risk factor for recurrence and death [1]. There is limited information in the literature about the clinicopathological characteristics of very young women with breast cancer. The aim of this report was to define the clinicopathological characteristics of very young women with breast cancer (≤ 25 years of age) followed in our institute.

Among 1,465 females with breast cancer, there were 16 (1.09%) very young patients (≤ 25 years of age) followed up between 2006 and 2009. All of them were premenopausal and living in urban areas at the time of diagnosis. The median age at diagnosis was 23 years (range 19-25) and median age at menarche 13 years (range 11-15). Median body mass index (BMI) was 25.3 kg/m² (range 16-38.5). Two patients (12.5%) had type I diabetes mellitus and another 2 were using antidepressants. Nine patients (64.2%) had history of cancer in the family. Family history of breast cancer was positive in 5 (31.2%) patients. Two of these (12.5%) had history of breast cancer in first-degree relatives. There were no special dietary habits and prior medication history of patients, and also no similarities in their employment. Histology revealed infiltrating ductal carcinoma and 4 patients (25%) had also infiltrating lobular carcinoma component; one patient (6.25%) had bilateral disease. Negative estrogen and progesterone receptors were found in 12.5% of the patients. Twenty-five percent of the patients had HER2/neu positive tumors (3^+ with immunohistochemistry or positive by fluorescent *in situ* hybridization). Triple negative disease was detected in one patient (6.25%). Lymphovascular and perineural invasion was detected in 31.2% and 18.7% of the patients, respectively. Grade 3 tumors were seen in 62.5% of the patients. The mean tumor size was 3.7 cm (range 1.7- 8). T2 (≤5 cm) disease was detected in 56.2% of the patients, and 62.5% of them were node-positive. The median patient follow up was 22 months (range 8-34). None of these patients developed distant metastasis, whereas 1 of 16 (6.25%) suffered local recurrence during the follow up period.

As mentioned previously age < 35 is an independent risk factor of recurrence and death in breast cancer patients [1]. Studies aiming at defining the clinicopathological characteristics and prognosis of young breast cancer patients (mostly ≤ 35 years of age) are found in the literature [2,3], but data with youngest breast cancer patients, especially ≤ 25 years of age, is very limited [4]. In our study we found that patients ≤ 25 years of age had more high grade, Her2/neu positive, and triple negative tumors compared to our institute's whole breast cancer population. Loss of nuclear BRCA-1 expression might be responsible for this specific tumor biology in very young breast cancer patients [5]. Family history of breast cancer was also frequent in our group of very young patients. In the study by Walker et al. the frequency of family history of breast cancer was 15% in breast cancer women <30 years [1]. Family history of breast cancer was more frequent (31.2%) in our patients aged ≤25 years compared with the results of the Walker et al. study [1] in which the incidence of family history of breast cancer was 11% in the under 35 years age group.

References

1. Walker RA, Lees E, Webb MB, Dearing SJ. Breast carcinomas occurring in young women are different. Br J Cancer 1996; 74: 1796-1800.
2. Eralp Y, Smith TL, Altundag K et al. Clinical features associated with a favorable outcome following neoadjuvant chemotherapy in women with localized breast cancer aged 35 years or younger. J Cancer Res Clin Oncol 2009; 135: 141-148.
3. Aksoy S, Bulut N, Dizdar O et al. Pathological characteristics of very young (< or = 30 years) breast cancer patients: a single-institution experience from Turkey. Ann Oncol 2009; 20: 790.
4. Dobi A, Kelemen G, Kaizer L et al. Breast Cancer under 40 Years of Age: Increasing Number and Worse Prognosis. Pathol Oncol Res 2010 Sep 17. [Epub ahead of print]
5. Lee WY. Frequent loss of BRCA1 nuclear expression in young women with breast cancer: an immunohistochemical study from an area of low incidence but early onset. Appl Immunohistochem Mol Morphol 2002; 10: 310-315.

E. Ararat, I. Sahin, C. Arslan, S. Aksoy, O. Dizdar, Y. Ozisik, K. Altundag

Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey

Correspondence to: Kadri Altundag, MD. E-mail: altundag66@yahoo.com

Percentage of family history of cancer in patients with breast cancer: Is it changing with ethnicity?

Dear Editor,

We read with great interest the article of Andjelic-Dekic et al. [1] on the family history of cancer in patients with various types of cancer. Among 677 newly diagnosed cancer patients with 9 cancer types, positive family history (at least one first-degree relative) for any kind of cancer was recorded in 163 (24.1%) patients and in 47 (6.9%) patients for the same cancer type. The highest percentage of positive family history for the same type of cancer was encountered in patients with breast cancer (9.9%), followed by colorectal (7.2%) and brain tumors (6.25%). We have also retrospectively analyzed the family history of any cancer in first- and second-degree relatives of patients with breast cancer. Among 1218 patients with breast cancer, 598 (49.1%) had at least one first- or second-degree relative with any cancer, including 183 (15%) with breast cancer, 108 (8.8%) with lung cancer, 63 (5.2%) with colorectal cancer, 54 (4.4%) with gastric cancer, 37 (3%) with hematological malignancies, and 33 (2.7%) with prostate cancer. When the first-degree relatives of the patients were analyzed, we observed that 348 patients (28.6%) had at least one first-degree relative with cancer. The cases consisted of 82 patients (6.7%) with breast cancer, 62 (5.1%) with lung cancer, 33 (2.7%) with colorectal cancer, 22 (1.8%) with gastric cancer, 21 (1.7%) with hematological malignancies and 15 patients (1.2%) with prostate cancer. Our results considering family history of breast cancer in patients with breast cancer are slightly lower than the results of Andjelic-Dekic et al. (6.7 vs. 9.9%, respectively) and than the results of a huge meta-analysis (6.7 vs. 7.3%, respectively) [2]. Family history of cancer is used to estimate the risk of future cancer development, particularly in patients with breast and colorectal cancer. As seen in these studies, family history of cancer may show variations among different ethnicities and countries. Thus the relative risk of cancer may not be uniform in individuals with different ethnicities when they have a positive family history of cancer.

References

1. Andjelic-Dekic N, Tomasevic Z, Milosevic S, Kolarevic D, Jelic S. Do we know how many cancer patients have a family history of cancer? J BUON 2010; 15: 127-130.
2. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001; 358: 1389-1399.

O. Dizdar, C. Arslan, K. Altundag

Department of Medical Oncology Hacettepe University Institute of Oncology, Ankara, Turkey

Correspondence to: Kadri Altundag, MD. E-mail: altundag66@yahoo.com

Carcinomatous meningitis from transitional cell carcinoma of the urinary bladder

Dear Editor,

Carcinomatous meningitis (CM) is an important clinical complication of malignant tumors, occurring in approximately 5% of all patients with cancer. CM is pleomorphic in its clinical presentation as it affects all levels of the central nervous system (CNS) [1]. Transitional cell carcinoma (TCC) of the urinary bladder accounts for approximately 2% of all malignant tumors [2]. The tumor usually spreads through both local invasion and hematogenous dissemination. CNS metastases have been estimated to occur in 0.4-12% of patients with TCC [3,4]. Although intraparenchymal brain metastases occur in patients who have received combination chemotherapy, CM has rarely been reported.

Herein, we report the case of a 67- year-old man with TCC, who developed CM two months after completion of combination chemotherapy for advanced disease. The patient presented with painless hematuria in 1998. Cytoscopy showed a bladder tumor which

was resected, and histology revealed the presence of a superficial transitional cell papilloma. Intravesical treatment with BCG followed the transurethral resection. The patient was well until February 2003, when hematuria recurred. Cytoscopic examination showed a large sessile mass invading the left ureter and biopsy revealed muscle-invasive, high grade TCC extending into the perivesical fat (pT3). Evaluation for metastatic disease showed diffuse para-aortic and iliac lymphadenopathy. Because of borderline renal function the patient started chemotherapy with intravenous carboplatin at AUC 6 on day 1, methotrexate 30 mg/m^2 and vinblastine 4 mg/m^2, both administered intravenously on days 1 and 8. Cycles were repeated every 3 weeks. Although lymphadenopathy appeared to have subsided after 6 courses of chemotherapy a computed tomography scan revealed a pelvic mass, possibly invading the sacral bone. After 2 months of treatment the patient displayed neurologic disorders. Specifically, he presented neck stiffness followed by peripheral neuropathy, loss of plantar reflexes, alterations of the mental status, and signs of depression. A cerebrospinal fluid examination was performed which confirmed CM. The patient died because of septic shock due to lower respiratory infection, most likely aspiration pneumonia, caused by his lethargic situation 9 days after his admission to our hospital. He received only one dose of 12.5 mg intrathecal methotrexate.

Although CM is an important clinical problem in oncologic patients and especially in those who have advanced-stage disease, TCC of the urinary bladder rarely complicates the nervous system. In our case, a pelvic mass possibly invading the sacral bone seemed to be the path through which carcinomatous cells invaded the nerves and finally reached the meninges. Identification of a neurologic deficit or symptom in a bladder carcinoma patient should be followed by a focused investigation. The disease can affect any level of the CNS, and should thus be taken into consideration by the clinician when a patient presents with any of the usual clinical characteristics of CM.

References

1. Marc C. Chamberlain. Neoplastic meningitis: a guide to diagnosis and treatment. Curr Opin Neurol 2000; 13: 641-648.
2. Anderson TS, Regine WF, Kryscio R, Patchell RA. Neurologic complications of bladder carcinoma: a review of 359 cases. Cancer 2003; 97: 2267-2272.
3. Bishop JR, Moul JW, Mandonado L, Mcleo DG. Transitional cell carcinomatous meningitis after M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy. Urology 1990; 36: 373-3737.
4. Raghavan D, Chye RWM. Treatment of carcinomatous meningitis from transitional cell carcinoma of the bladder. Br J Urol 1991; 67: 438-440.

E. Kastritis, F. Zagouri, M-A. Dimopoulos, C.A. Papadimitriou

Department of Clinical Therapeutics, "Alexandra" Hospital, University of Athens School of Medicine, Athens, Greece

Correspondence to: Christos A. Papadimitriou. E-mail: chr_papadim@yahoo.gr

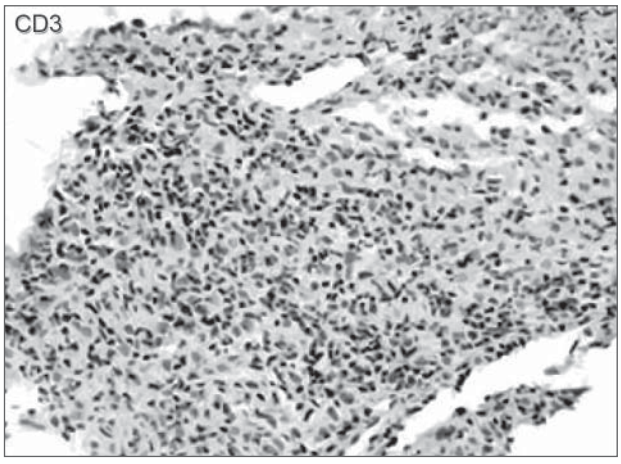
Hepatitis B surface antigen seroreversion in a T-cell lymphoma patient

Dear Editor,

It is known that cancer patients who are carriers of the hepatitis B virus (HBV) frequently present with complications of HBV reactivation during chemotherapy. Furthermore several studies have reported hepatitis B surface antigen (HBsAg) seroreversion in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1,2], in human acquired immunodeficiency virus (HIV)-infected patients with detectable HBV DNA after withdrawal of lamivudine [3], and patients with B-cell-clone hematopoietic malignancy receiving chemotherapy associated with rituximab in the absence of prophylactic antiviral therapy [4].

A 77-year-old man presented with multiple nontender masses over the right neck which were examined by fine needle aspiration cytology showing T-cell lymphoma. Full staging work up revealed stage IIIb angioimmunoblastic T-cell lymphoma (Figure 1). Cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) was initiated. On admission the patient exhibited elevated SGOT and SGPT levels. Hepatitis screen revealed HBsAg seroreversion and HBV reactivation (Table 1). Following treatment with entecavir, SGOT and SGPT levels reduced and hepatitis symptoms (easy fatigue and general malaise) improved.

Current treatment guidelines state that for patients who are at risk of HBV reactivation, prophylactic anti-



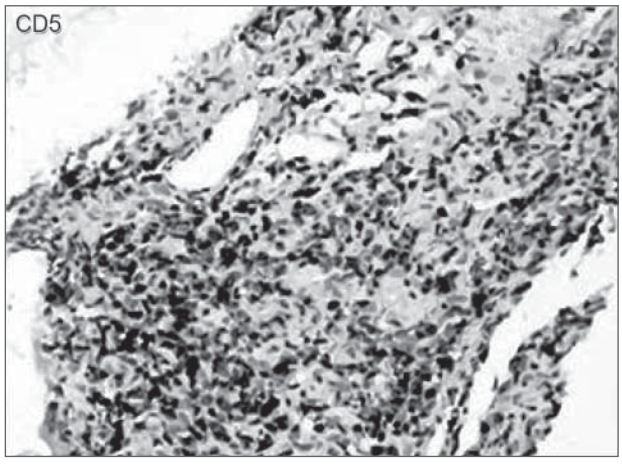


Figure 1. Tumor cells showing positive nuclear immunoreaction by CD3 and CD5 (H&E ×400).

Table 1. Comparison of hepatitis B virus screen before and after chemotherapy

	HBsAg	*HBeAg*	*Anti-HBs*	*Anti-HBe*	*Anti-HBc*	*Anti-HCV*	*Viral load (cps/mL)*
Pre-chemotherapy	–	–	+	–	+	–	–
Post-chemotherapy	+	+	–	–	+	–	56000

viral treatment should be administered prior to chemotherapy in order to avoid severe hepatic injury. There are several studies revealing HBsAg seroreversion in HSCT recipients, indicating that subjects with chronic hematological diseases are at a high risk of HBV reactivation. AIDS patients can also exhibit HBsAg seroreversion even decades after full recovery from acute hepatitis B with lamivudine due to progressive immunodeficiency. Patients with B-cell-clone hematopoietic malignancy have also been reported to present with HBsAg seroreversion during chemotherapy. Cellular and humoral immunity work together to suppress HBV reactivation. The long-term memory of HBsAb may be maintained by chronic production of serologically undetectable amounts of antigen, due to persistent HBV infection after recovery from acute hepatitis B. In immunocompromised patients, the defect in cellular or humoral immunity will lead to disruption of HBsAb production; thus, the HBV will reactivate with the presentation of HBsAg seroreversion. In HSCT recipients, chemotherapy leading to B-cell dysfunction in producing HBsAb may be the cause of HBsAg seroreversion. When $CD4^+$ T-cells of HIV-infected patients with AIDS are destroyed, B cells are affected significantly, leading to HBsAb malproduction and consequently increasing the risk of HBsAg seroreversion. When patients with B-cell-clone hematopoietic malignancy receive chemotherapy, especially with rituximab, the B-cells will be directly disrupted and HBsAb production will be significantly affected. In our study, the T-cell lymphoma patient receiving chemotherapy also presented with HBsAg seroreversion. This may be due to T-cell functional impairment leading to B-cell dysfunction and disruption of HBsAb production. After the consumption of HBsAb, the HBV viral load will increase and the HBsAg will be positive. Recently, the anti-CD20 target chemotherapy agent rituximab, which induces profound and durable B-cell depletion, has played an important role in the treatment of diffuse large B-cell lymphoma; however, it is predictive of HBV reactivation [5].

To our knowledge, this case is the first to demonstrate the possible occurrence of HBsAg seroreversion in a T-cell lymphoma patient. With the increasing use of rituximab, the clinicians are faced with increasing clinical challenges from HBV reactivation, especially in endemic areas.

References

1. Viganò M, Vener C, Lampertico P et al. Risk of hepatitis B surface antigen seroreversion after allogeneic hematopoietic SCT. Bone Marrow Transplant 2011; 46: 125-131.
2. Knoll A, Boehm S, Hahn J, Holler E, Jilg W. Long-term surveillance of haematopoietic stem cell recipients with resolved hepatitis B: high risk of viral reactivation even in a recipient with a vaccinated donor. J Viral Hepat 2007; 14: 478-483.

3. Altfeld M, Rockstroh JK, Addo M et al. Reactivation of hepatitis B in a long-term anti-HBs-positive patient with AIDS following lamivudine withdrawal. J Hepatol 1998; 29: 306-309.
4. Tsutsumi Y, Tanaka J, Kawamura T et al. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol 2004; 83: 58-60.
5. Yeo W, Chan TC, Leung NW et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009; 27: 605-611.

Hsuan-Wei Chen[1], Shine-An Lin[1], Hsin-Chung Lin[2], Woei-Yau Kao[3]

[1]Department of Internal Medicine; [2]Department of Pathology; [3]Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan

Correspondence to: Woei-Yau Kao, MD, PhD. E-mail: wykaodr@gmail.com

Long term survival in a metastatic alveolar soft part sarcoma at the time of diagnosis: a case with 17 years of follow-up

Dear Editor,

Among all soft tissue sarcomas, alveolar soft part sarcoma (ASPS) is rare with an incidence of 0.5-1% and most commonly presented as a mass in lower extremities [1]. ASPS is slow growing tumor [2]. The overall survival is long with an average of 36 months, even though in metastatic stage compared to other sarcomas [3].

A 17-year-old male patient was referred to our hospital complaining of left hip pain in September 1992. His physical examination showed a mass in the left gluteal region. Radical tumor excision was performed which showed ASPS. Thoracic computerized tomography (CT) revealed multiple metastases. Chemotherapy with VAC (cyclophosphamide, actinomycin D and vincristine) every 3 weeks was initiated and given for 27 months until January 1995. Chemotherapy resulted in stabilization of the lung lesions.

Then, 5 courses of IMA (ifosfamide, mesna, adriamycin) were administered between March and July 1995. However, due to progression of pulmonary lesions 4 cycles of cisplatin and etoposide were administered between September 1995 and March 1996. Due to new progression of pulmonary metastases, dacarbazine and adriamycin chemotherapy was initiated in May 1996. Since the cumulative dose of adriamycin was reached, the treatment was discontinued at the end of the second cycle and a drug-free follow up was decided.

The patient was readmitted to our hospital with headache and diplopia in December 2007. A cranial magnetic resonance imaging (MRI) revealed a mass measuring 60×62×42 mm, located deep in the white matter of the left posterior-parietal area which was totally excised. Histological examination was consistent with metastatic ASPS. Whole brain palliative radiotherapy to a total dose of 30 Gy in 10 fractions was delivered with a boost of 12.5 Gy in 5 fractions to the tumor bed. In October 2009, a minimal progression of the pulmonary lesions was observed; it was decided to continue the patient's follow-up without chemotherapy.

According to the literature, the median survival time and 5-year survival rate are 3-3.3 years and 20% in metastatic patients, respectively [1,2]. Portera et al. reported a median survival of 40 months in patients with M1 disease [1]. Our patient has been alive for 17 years despite pulmonary metastases detected at diagnosis and brain metastases 15 years after diagnosis. These data make our case unique.

Metastasis at the time of diagnosis is associated with poor prognosis. The time interval from diagnosis to metastases is over 5 years in only 10% of patients with ASPS [3]. ASPS generally metastasizes to the lung, bone and brain [4]. in a large series of asps, 65% of all cases were metastatic at first presentation. In that study, the most common and usually the only site of metastases was lung, whereas the rate of brain metastasis was only 19% [1].

Metastases to the brain in patients with ASPS are 3-fold more common than those of other soft tissue sarcomas. Resection of brain metastases provides improvement in overall and progression-free survival [2]. In the present case, brain metastases were detected 15 years after the diagnosis and metastasectomy was performed. Therefore, this case is extremely rare with its long interval between two metastatic localizations compared to other similar cases in the literature.

References

1. Portera CA Jr, Ho V, Patel SR et al. Alveolar soft part sarcoma:

clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer 2001; 91: 585-591.
2. Benetos IS, Mavrogenis AF, Soultanis KCh et al. Alveolar soft part sarcoma of the forearm: a case report. J Surg Orthop Adv 2006; 15: 209-213.
3. Kayton ML, Meyers P, Wexler LH et al. Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults. J Pediatr Surg 2006; 41: 187-193.

F. Tugba Kos[1], D. Uncu[1], B. Oksuzoglu[2], S. Aksoy[1], N. Ozdemir[1], H. Odabas[1], M. Isik[1], B. Civelek[1], N. Zengin[1]

[1]Ankara Numune Training and Research Hospital, Department of Medical Oncology, Ankara; [2]Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey

Correspondence to: Sercan Aksoy, MD. E-mail: saksoy07@yahoo.com

How addition of capecitabine might be more beneficial in the neoadjuvant treatment of breast cancer

Dear Editor,

The demonstrated effectiveness of capecitabine in the metastatic setting supports its integration in the treatment of early breast cancer. This evidence is also accompanied by a favorable safety profile, with minimal myelosuppression and alopecia. Neoadjuvant chemotherapy is widely accepted as a treatment option for patients who are later candidates for adjuvant chemotherapy [1]. Current guidelines recommend the use of anthracyclines and taxanes. The study by von Minckwitz et al. [2] regarding the effect of capecitabine in addition to anthracycline-and taxane-based neoadjuvant treatment in patients with primary breast cancer compared the pathological complete response (pCR) rate between concomitant (epirubicin [E]+ cyclophosphamide [C] plus docetaxel + capecitabine) and sequential addition of capecitabine (E+C plus docetaxel plus capecitabine) and a regimen without capecitabine (E+C plus docetaxel). They found that adding capecitabine to or prolonging the duration of neoadjuvant EC plus docetaxel failed to demonstrate higher efficacy at surgery. We would like to speculate about why the addition of capecitabine to standard regimens did not achieve a higher pCR rate. A recently published randomized controlled trial by Joensuu et al.[3] showed that capecitabine-containing chemotherapy reduced breast cancer recurrence compared with a control schedule of standard agents. They used 8 cycles of capecitabine 1800 mg/m^2 in contrast to the study of von Minckwitz et al. [2] in which 4 cycles of capecitabine 1800 mg/m^2 were used. Thus, the significant efficacy of capecitabine in the study by Joensuu et al. [3] could be depended on the total dose of capecitabine. Moreover, Joensuu et al. [3] used taxane first, followed by anthracycline as a standard regimen, whereas in the study of von Minckwitz et al. anthracycline was used first, followed by a taxane. Wildiers et al. [4] mentioned that the administration of taxane first, followed by an anthracycline, may be favorable in terms of pCR. Therefore, this sequencing might affect the efficacy of capecitabine through unknown mechanisms. In conclusion, higher dose of capecitabine and/or administration of a taxane first, followed by an anthracycline might be associated with higher efficacy of neoadjuvant chemotherapy in achieving pCR.

References

1. Kaufmann M, Hortobagyi GN, Goldhirsch A et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: An update. J Clin Oncol 2006; 24: 1940-1949.
2. von Minckwitz G, Rezai M, Loibl S et al Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III GeparQuattro Study. J Clin Oncol 2010; 28: 2015-2023.
3. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R. Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for breast cancer: an open-label, randomised controlled trial. Lancet Oncol 2009; 10: 1145-1151.
4. Wildiers H, Forceville K, Paridaens R, Joensuu H. Taxanes and anthracyclines in early breast cancer: which first? Lancet Oncol 2010; 11: 219-220.

E. Ararat, I. Sahin, K. Altundag

Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey

Correspondence to: Kadri Altundag, MD. E-mail: altundag66@yahoo.com