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LETTERS TO THE EDITOR

Triple negative endometrial cancer may be more sensitive to platinum based chemotherapy

Dear Editor,

Endometrial cancer is the most common gynecologic cancer in the developed world. In 2011, the mortality rate was 1.7-2.4 per 100,00 women. In the United States, as with other developed countries, 46,470 new cases and 8,120 deaths were due to this disease in 2011 [1,2]. Endometrial cancer is divided into type I and II subtypes. Type I is associated with a hyperestrogenic state and usually occurs in obese women, tend to be well differentiated and is identified in early stages. Type II, which is not associated with hyperestrogenism, is usually seen in thin women and is diagnosed in advanced stages. Most endometrial cancers are low-grade, early-stage and carry an excellent prognosis. On the other hand, the 5-year survival of advanced stages (stage 3 and 4) ranges between 23 and 67%.

Breast cancer is also one of the most frequent malignancies in women. The lifetime risk for breast cancer in the United States is usually about 1 in 8 (12%) of women by the age of 95, with 1 in 35 (3%) chance of dying from breast cancer [3]. Breast cancer can be divided in subgroups based on immunohistochemical staining. The group that lacks estrogen receptor (ER) and progesterone receptor (PR) expression and shows absence of HER2 protein overexpression is known as the triple negative phenotype (TNP). TNP breast cancers are more aggressive, have a high proliferation rate, high nuclear grade, frequent p53 overexpression, are more likely to show distant metastasis, and have poorer outcomes, including shorter disease-free and overall survival [4]. TNP breast cancer (TNBC) cells exhibit an abundance of DNA aberrations, suggesting that their DNA repair mechanisms are defective. Consequently, these tumors are theorized of having an increased sensitivity to agents that cause interstrand DNA breaks (e.g., platinum agents). As such, the sensitivity of TNP breast cancers to platinum-based chemotherapy has been the focus of several recent clinical trials in the neoadjuvant/adjuvant and advanced disease settings. A study conducted by Sirohi et al. has retrospectively evaluated the efficacy of platinum-based drugs in 143 metastatic breast cancer patients. Among these, 93 (63.7%) were TNP. The objective response rate was 33.3% in the TNBC group vs. 22% in the non-TNBC (p=0.1) although no difference in OS, PFS and response duration was observed [5]. To summarize, as platinum-based treatments are effective in TNBC, we expect them to be also effective in TNP endometrial cancer. Larger studies conducted in such TNP populations to search effectiveness of platinum-based chemotherapy are needed.

References

1. Jemal A, Bray F, Center MM et al. Global Cancer Statistics. CA Cancer J Clin 2011; 61:69-90.
2. Siegel R, Ward E, Brawley O, Jemal A. Cancer Statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61:212.
3. Howlader N, Noone AM, Krapcho M et al (Eds): SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
4. Reis-Filho J, Tutt AM. Triple negative tumours: a critical review. Histopathology 2008; 52: 108-118.
5. Sirohi B, Arnedos M, Popat S et al. Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol 2008; 19: 1847-1852.

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High dose chemotherapy with autologous stem cell transplantation for patients with germ-cell cancer

Dear Editor,

Germ cell tumors (GCTs) practically represent the only kind of solid tumors that are curable by chemotherapy even when metastatic. This is largely due to their chemosensitivity. Although most of these tumors are cured with the first – or - second-line chemotherapy, patients who experience more than two relapses, or are refractory to all therapy lines, usually die from this disease. The bad prognosis of these patients had urged researchers to search for other treatment options, and having in mind the chemosensitivity of GCTs, a logical step was to increase the doses of cytotoxic drugs and try to overcome the resistance with high-dose therapy [1]. In a retrospective study published in 2008 Einhorn et al. stressed that high-dose protocols for metastatic GCTs can cure a certain number of patients even after multiple relapses [2]. After the publication of this study, our Institute also introduced this procedure using a modified TAXIF protocol of the Tenon hospital, Paris [3,4]. The final confirmation of the activity of high-dose chemotherapy was the last year's retrospective study by Lorch et al. [5] where in 1984 patients they proved that in relapsed GCTs high-dose therapy, followed by autologous hematopoietic stem cell transplantation leads to longer survival when compared to conventional chemotherapy.

During 2008-2010 we performed 11 transplantations in 8 heavily pretreated patients who were previously administered a median of 4 (range 3-4) chemotherapy lines. We used a modified TAXIF protocol, which includes mobilization of stem cells by administering the submyeloablative protocol paclitaxel 250 mg/m^2 and epirubicin 100 mg/m^2 with G-CSF 10 mcg/kg. After mobilization, a large-volume apheresis was performed until the harvested number of cells was enough for two transplantations. The high-dose protocol was the combination of carboplatin AUC 4 daily for 5 days plus etoposide 300mg/m^2/day, days 1-5. The median number of the administered stem cells per transplantation was 3.6x109 (range 1.9-4.5) CD34+ cells per kg of body weight. The median time for neutrophils engraftment was 10 days, and for thrombocytes 13 days. There were no therapy-related deaths. The most frequent grade 3 / 4 toxicities were febrile neutropenia (100% of patients), thrombocytopenia (100%), colitis / diarrhea (63%), nausea (54%) and oral mucositis (45%). One patient developed veno-occlusive liver disease, while 2 patients developed grade 4 infections (facial phlegmon and one septic shock). Overall clinical benefit rate was 62.5% (37.5% PR, 25% SD). No complete remissions were seen. Median survival was 11 months (range 4-20). High-dose chemotherapy with stem cell transplantation represents an option for heavily pretreated patients with GCTs and is feasible at our Institute, which may be one of the reference centers for this kind of treatment in the Balkans. The treatment results in this group of patients is poor, so earlier intensification is mandatory.

References

1. Krege S, Beyer J, Souchon R et al. European Consensus Conference on Diagnosis and Treatment of Germ Cell Cancer: A Report of the Second Meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): Part II. Eur Urol 2008; 53: 497-513.
2. Einhorn L, Williams S, Chamness A, Brames R, Perkins S, Abonour R High-dose chemotherapy and stem cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-348.
3. Lotz JP, Bui B, Gomez F et al, on behalf of the Groupe d'Edutes des Tumeurs Uro-Genitales (GETUG). Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of phase II multicentric TAXIF trial. Ann Oncol 2005;16:411-418.
4. Popovic L, Jovanovic D, Donat D, Petrovic D, Roganovic T, Lotz

JP. High-dose chemotherapy with autologous stem cell support for heavily pretreated patients with germ cell tumors: a Serbian single-centre first-experience report. Bone Marrow Transpl 2011; 46 (Suppl 1): 385.

5. Lorch A, Bascoul-Mollevi C, Kramar A et al. Conventional-Dose Versus High-Dose Chemotherapy As First Line Salvage Treatment in Male Patients with Metastatic Germ-Cell Tumors: Evidence From a Large International Database. J Clin Oncol 2011; 29: 2178-2184.

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Colon involvement in a chronic lymphocytic leukemia patient

Dear Editor,

Chronic lymphocytic leukemia (CLL) is the most frequently observed type of leukemia in patients older than 50 years. The prognosis of this disease is much better when compared to other leukemia types [1]. Although CLL primarily involves the bone marrow, extramedullary tissues may also be affected. In CLL patients, gastrointestinal involvement is usually seen in Richter syndrome, which is the disease transformation into large B cell lymphoma [2]. The prognosis worsens in such cases.

A 61-year-old woman presented to our outpatient department with stomach ache in the midline. Physical examination revealed no lymphadenopathy or hepatosplenomegaly. Lab tests revealed white blood cell count 25890 mm^3, lymphocyte count 18290 mm^3, hemoglobin level 14.2 g/dl, platelet count 208000 mm^3, lactate dehydrogenase level 454 IU/dl, while peripheral blood smear demonstrated 72% mature lymphocytes with occasional basket cells. Bone marrow aspiration and biopsy were performed and were consistent with CLL (60% B lymphocytes, CD 20 (+), CD 79 (+), CD5 (+)). A flow cytometry performed showed CD5 90% CD23 80%, indicating that the sample comprised of leukemic cells. Abdominal CT scan revealed thickening of the wall of the transverse colon, after which a colonoscopy was performed. In colonoscopy, the transverse colon mucosa was, in general, minimally edematous, granular and in the rectum there were numerous apparent Peyer plaques. Biopsies were obtained from the rectum and transverse colon which were consistent with chronic lymphocytic colitis. Microscopically, dense mucosal and submucosal lymphocytic infiltrates were detected in the transverse colon, and 4/7 biopsies of the colon, showed predominance of small CD20 positive lymphocytes. The cells stained positively also for CLL-associated antigens CD5, CD23, and CD43, but were negative for mantle cell-associated antigen cyclin D1. The patient was considered stage 0 CLL with colon involvement. Gastrointestinal involvement is not common in CLL. Colon involvement without Richter syndrome has rarely been reported in the literature. Arkila et al. [3] have reported a 69-year-old man with CLL and anemia in whom colonoscopy was macroscopically normal, but the histological specimens revealed lymphocytic leukemia in the ileum and colon. In our patient we also have demonstrated colon involvement without Richter syndrome. CLL may cause upper gastrointestinal haemorrhage by directly infiltrating the gastroesophageal junction or through bleeding from oesophageal varices caused by CLL-associated splenomegaly and portal hypertension. According to one case report [4], protein-losing enteropathy may be found in CLL patients. Reports also mention gastrointestinal CLL manifestations such as infiltration of the intestinal mucosa in the small bowel as well as CLL presenting as colitis. CLL, especially after Richter transformation, can cause signs and symptoms suggestive of chronic inflammatory bowel disease. Other rarely described CLL manifestations include intussusception, even perforation of the colon and can also form a route

for infectious complications. The histopathologic differential diagnosis of common benign lymphatic hyperplasias and various malignant lymphoid disorders of the intestine may be challenging. The diagnostic range for CLL should include CD20+/CD5+ coexpression with CD23+ phenotype, and negative staining pattern for Cyclin D1 to exclude mantle cell lymphoma. Differential diagnosis of indolent CD5 negative B-cell lymphomas include follicular lymphoma, which usually has CD10+ phenotype, whereas mucosa-associated marginal zone lymphoma lacks specific phenotypic markers and its immunophenotypic diagnosis is mainly based on exclusion. Lymphoepithelial lesions and plasmacytic differentiation are suggestive of MALT-lymphoma [5].

In conclusion, also gastrointestinal evaluation should perhaps be part of a complete assessment of the treatment response and remission status in CLL patients in whom the colon was originally involved. In CLL patients with gastrointestinal symptoms, an endoscopic evaluation must be performed, and biopsies must be obtained from suspicious regions. The fact that CLL patients may have gastrointestinal involvement without Richter syndrome must be kept in mind.

References

1. Montserrat E, Rozman C. Chronic Lymphocytic Leukemia: Prognostic factors and natural history. Baillieres Clin Hematol 1993;6: 849-866.
2. Robertson LE, Pugh W, O'Brien S et al. Richter's syndrome. A report on 39 patients. J Clin Oncol 1993; 11: 1985-1989.
3. Arkkila PET, Nuutinen H, Ebeling F et al. Colonic Involvement in a Patient with Chronic Lymphocytic Leukaemia. Gastroenterol Res Pract 2008; 742146.
4. Obata S, Matsuzaki H, Nishimura H et al. Gastroduodenal complications in patients with adult T-cell leukemia. Jpn J Clin Oncol 1988;18: 335-342.
5. Romaguera J, Hagemeister FB. Lymphoma of the colon. Curr Opin Gastroenterol 2005; 21:80-84.

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A simple technique for vacuum drainage of the peritoneal cavity for the management of anastomotic leaks in patients with gastrointestinal malignancies

Dear Editor,

In cancer patients, any anastomosis along the gastrointestinal tract carries the risk of an anastomotic leak, the incidence of which can be as high as 20%, depending on several and specific local and systematic factors [1]. Following an anastomotic leak, the content of the gastrointestinal tract accumulated into the peritoneal cavity can lead to generalized peritonitis, intraperitoneal abscess formation or it can be drained through the abdominal wound, predisposing to abdominal wall infection and wound dehiscence. Sometimes gravity is not enough for the drainage of the accumulated content and the application of a negative pressure has been proposed as an effective method for the drainage of anastomotic leaks [2].

Between January 2005 to December 2010, 6 patients who were operated on either electively or as an emergency for gastrointestinal tract malignancies and developed gastrointestinal anastomotic leak, were treated with a simple technique for vacuum drainage of the peritoneal cavity after the diagnosis of gastrointestinal leak. In all cases the edge of either the silicon or the PVC tubes was connected to the vacuum pump system (Basic 30 Aspirator, Medela, Illinois, USA) and -20kPa (-150 mm Hg) negative pressure was applied. The -20kPa vacuum pressure was chosen, since we noticed that greater pressures collapsed the lumen of the silicon tubes. We also noticed that the simple connection of the cannula of an ileostomy

Table 1. Details of the gastrointestinal leaks and the application of the proposed vacuum system

Sex/Age (years)	*Brief clinical history*	*Diagnosis of leak*	*Period of VS application (days)*	*Type of fistula finally formed*	*Healing of the fistula (weeks)*
M/86	Disseminated descending colon cancer. Palliative procedure	Enteric content through the intra-operatively placed drain tube and the surgical incision	5	Entero-cutaneous	8
M/54	Splenic flexure colon cancer. Curative operation	Smelly gas but no faecal content through the drain tube	2	Feacal-cutaneous	2
M/51	Disseminated descending colon cancer. Palliative procedure	Enteric content through the lower third of the surgical incision	6	Entero-cutaneous	14
M/62	Cecal adenocarcinoma. Curative operation	Abdominal CT scan revealed a subhepatic abscess infiltrating the right lateral abdominal wall	3	Entero-cutaneous	8
M/75	Pancreatic head adenocarcinoma. Curative operation	Bile through the upper third of the surgical incision	3	Bilio-cutaneous	4
M/77	Rectosigmoid junction cancer. Curative operation	The three lowermost metallic staples for skin approximation were removed leaving a 3cm cutaneous opening	4	Feacal-cutaneous	4

M: males, VS: vacuum system

bag to the vacuum system was similarly insufficient, since the application of even the minimum vacuum pressure (-9kPa) collapsed the bag. Thus, in cases of enteric content drainage through the surgical incision we preferred the air-tightly secure placement of either PVC (N=2) or soft silicon drain tubes (N=1) via the colostomy bag up to the dermal gap and connection of the drain tubes to the vacuum system. With this technique the inflamed, ischemic or necrotic tissues of the abdominal wound were drained into the bag, while the gastrointestinal tract content was driven away of the wound into the vacuum system collector. The vacuum was applied continuously throughout the day and the gastrointestinal content output was recorded every 24 hours. The vacuum was disconnected when less than 30mL of gastrointestinal tract content drainage was recorded within 24 hours and when obvious improvement of the local signs of inflammation was noticed.

Patient characteristics, details of the gastrointestinal leaks and the application of the proposed vacuum system are shown on Table 1. All fistulae were healed spontaneously within 3-14 weeks (median 6). None of the patients developed generalized peritonitis, abscess formation or would dehiscence. A single fistula was successfully crated in all patients and none of the patients developed adverse events while all abdominal wounds were healed uneventfully.

Vacuum assisted closure (VAC) therapy represents a well-established effective treatment option for the treatment of infected wounds, traumatic open abdominal wounds, wounds with bone exposure, pressure ulcers, diabetic foot ulcers and ulcers arising from venous ectasia in the extremities. The method is contraindicated or should not be applied in unexplored or non-enteric fistulae, in wounds with necrotic tissue, in the treatment of osteomyelitis, over actively bleeding tissues, over wounds

being in contact with exposed blood vessels or organs, in previously irradiated or sutured vessels or organs, or in patients treated with anticoagulants [3]. However, the application of the negative pressure for the management of enterocutaneous fistulae arising within an open abdomen still remains controversial with various reports favoring [4] and other being against its use [5].

In conclusion, the application of low vacuum pressure on the distal end of either the intraoperatively placed silicon drain tubes or the newly placed PVC tubes can desirably lead to an enterocutaneous fistula formation through a single point, disrupting the unfavorable sequences of the leak.

References

1. Robson MC, Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. Curr Probl Surg 2001; 38: 71–140.
2. Cro C, George KJ, Donnelly J, Irwin ST, Gardiner KR. Vacuum assisted closure system in the management of enterocutaneous fistulae. Postgrad Med J 2002; 78: 364 –365.
3. Lopez MR, Campos GC, Perez BS, Sanchez AG, Aguilar GL, Navaro JA. Negative pressure therapy in wounds with enteric fistulas. Cir Esp 2009; 86: 29-32.
4. Reed T, Economon D, Wiersema Bryant L. Colocutaneous fistula management in a dehisced wound: a case study. Ostomy Wound Manag 2006; 52: 60-64.
5. Fisher JE. A cautionary note: the use of vacuum assisted closure systems in the treatment of gastrointestinal cutaneous fistula may be associated with higher mortality from subsequent fistula development. Am J Surg 2008; 196: 1–2.

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Frequency of thyroid disease among breast cancer patients: a descriptive study of breast cancer patients

Dear Editor,

Currently, there are numerous studies on the relationship between breast cancer and thyroid disorders. Although the exact mechanism of the relationship remains unclear, many studies have shown that thyroid diseases are common among women with breast cancer [1,2]. Some investigators have suggested increased breast cancer risk in patients treated for thyroid disorders, but others believe that there is no association between thyroid diseases and risk of breast cancer [3].The purpose of this descriptive study was to examine the frequency of thyroid disease among breast cancer patients and to compare patient and tumor characteristics in patients with and without thyroid disease.

We retrospectively analysed the medical records of breast cancer patients diagnosed between 2004 and 2012 in Hacettepe University, Institute of Oncology. We examined the frequency of patients with known thyroid diseases including hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis and multinodular goiter and searched patients with suspected thyroid diseases. We evaluated tumor size, tumor grade, estrogen and progesterone receptor status, HER-2 expression and histology of primary tumors. Pearson's chi-square test was used for statistical analysis. A value of $p<0.05$ was considered statistically significant.

Among 2218 patients with breast cancer, 445 (20.1%) cases with thyroid diseases were found. The majority had multinodular goiter (7.9%, N=177) and diffuse goiter (6.9%, N=153). The incidence of other thyroid disorders are shown in Table 1. There was no statistically significant difference in patient and tumor characteristics between patients with and without thyroid diseases.

The relationship and coincidence of breast cancer

Table 1. Distribution of thyroid diseases and thyroidectomy in breast cancer patients

Thyroid disease	*N*	*%*
Multinodular goiter	177	7.9
Diffuse goiter	153	6.9
Hashimoto's thyroiditis	20	0.9
Thyroid cancer	9	0.4
Toxic goiter	6	0.3
Thyroidectomy	124	5.6

with thyroid disorders is a subject of extensive debate. In a prospective study, prevalence of autoimmune thyroid disorders in Greek breast cancer patients was found to be higher (43.9%) than in patients with benign breast diseases (19%) and healthy controls (18.4%) [4]. Ron et al. reported that there was a significantly elevated risk of thyroid cancer following breast cancer and breast cancer following thyroid cancer [3].The results of our study also support their conclusion. Our study suggests a fairly frequent occurrence of thyroid disease among breast cancer patients. However, we could not find an association between the presence of a thyroid disorder and any tumor characteristic.

Breast cancer may share some similar etiologic features with thyroid disease. For instance, thyroid and breast, both are under the influence of similar hormones. On the other hand, estrogen may influence the development, physiology and pathology of human thyroid gland [5]. We did not check all breast cancer patients for thyroid disease, we evaluate only patients with known thyroid disease and patients with suspected thyroid disease so there might be an information bias in our study. Given the inconclusive evidence in the literature we believe that further analytical studies in larger populations are clearly warranted. Meanwhile, we suggest oncologists to check for thyroid disease in women with breast cancer.

References

1. Cengiz O, Bozkurt B, Unal B et al. The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women. J Surg Oncol 2004; 87: 19-25.
2. Ron E, Curtis R, Hoffman DA, Flannery JT. Multiple primary breast and thyroid cancer. Br J Cancer 1984; 49: 87-92.
3. Simon MS, Tang M-TC, Bernstein L et al. Do thyroid disorders increase the risk of breast cancer? Cancer Epidemiol Biomarkers Prev 2002; 11: 1574-1578.
4. Gogas J, Kouskos E, Tseleni-Balafuta et al. Autoimmune thyroid disease in women with breast carcinoma. Eur J Surg Oncol 2001; 27: 626-630.
5. Turken O, Narin Y, Demirbas S et al. Breast cancer in association with thyroid disorders. Breast Cancer Res 2003; 5: R110-113.

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