

**【Title】**

Refractory hemorrhagic cystitis associated with T-DM1 : a case report

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**【Abstract】**

Recently, clinical use of the newly developed drugs against molecular targets of the breast cancer, trastuzumab emtansine (T-DM1), is increasing. T-DM1 is expected to prolong disease free survival and overall survival of locally advanced or metastatic HER-2 positive breast cancers. However, the adverse events, such as thrombocytopenia, severe hemorrhage and others, which are ascribed to T-DM1, have been reported. We report a patient who showed refractory severe hemorrhagic cystitis during the administration of T-DM1. A 60-year-old woman underwent a total mastectomy and axillary nodes dissection for the breast cancer in 2005, and received adjuvant therapy with doxorubicin, cyclophosphamide (CPA) and docetaxel. Multiple metastatic lesions were found in 2011, and then she received chemotherapy including capecitabine, CPA and trastuzumab. During the therapy, she noticed hematuria which soon disappeared spontaneously in September, 2013. For that reason, the patient never complained hematuria until T-DM1 was used. T-DM1 administration was initiated in February 2014, but was discontinued because of thrombocytopenia and severe hemorrhagic cystitis. Although T-DM1 is highly expected as a new therapeutic drug for HER2-positive breast cancer, we should grasp patients' therapeutic history in detail and evaluate the risk for the adverse events of the drug carefully.

An effective paclitaxel plus bevacizumab therapy for locally advanced breast cancer with malignant wound: a case report

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A 72-year-old female visited our hospital due to a tumor of 8 cm in diameter in her left breast with skin ulceration. Triple negative breast cancer with axillary lymph node metastasis was diagnosed. Four cycles of paclitaxel + bevacizumab therapy were administered, and her tumor almost disappeared. A mastectomy with axillary lymph node dissection was performed, immediately large skin defect of her left chest wall was reconstructed with latissimus dorsi flap. Her postoperative course was good. Thus chemotherapy with bevacizumab or extended chemotherapy is generally not considered to contribute to a survival improvement. However, such therapy contributes in increasing the response to chemotherapy, and should be considered for patients with locally advanced breast cancer to shrink the local lesions and improve the quality of life.

## One case of primary breast signet ring cell carcinoma

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Breast signet ring cell carcinoma is characterized by retention of mucus in within the cells. [Patient] 98-years-old, female. In late May, 2014, her right breast tumor was found by facility staff and she visited our hospital early in June on referral from her primary care doctor. By physical examination, we could touch 3 cms-tumor in her right breast BED area. By mammography, high density tumor was found under her right nipple and thought to be category 4. By ultrasonography, the tumor was 30 mm in diameter and looked like an intracystic tumor, internal inhomogeneous. There was an echo-free-space in the tumor and a solid space having much blood flow. Core needle biopsy diagnosed it as signet ring cell carcinoma. By PET-CT, we thought not so much gastric cancer as primary breast cancer. There was no metastasis. Because she had profound dementia, we could not check her will and made a decision of no operation due to her family will of no aggressive management. In mid-June, she started to take anastrozole by mouth. The tumor is getting smaller in January, 2015.

[Discussion] As we experienced one case of primary breast signet ring cell carcinoma, we report our case with the inclusion of bibliographic consideration.

Invasive solid papillary carcinoma: a case report.

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Solid papillary carcinoma (SPC) is rare tumor proposed by Maluf in 1995. Pathologically, SPC shows nodular and solid proliferation in duct, and the cells are low-grade malignancy. Immunohistochemically, SPC often has neuroendocrine or mucinous features.

A 46-year-old woman, a mass was detected in left breast and got larger gradually. By ultrasonography, the mass was visualized as a flat tumor in A portion of the breast, and the size was about 10 mm. Core needle biopsy was performed to this and showed atypical cells proliferated by solid pattern in ducts. Although It didn't include invasive lesion, myoepithelial markers(CD10, p63 and  $\alpha$ -SMA) were negative. Besides, neuroendocrine markers(NSE, chromogranin and synaptophysin) were positive. We diagnosed this tumor SPC from immunostaining report, and resected her left breast partially with sentinsel lymph node biopsy. Final diagnosis was SPC with massive SPC, because invasive component was seen in resected specimen.

SPC accounts for 1.7% in all breast carcinomas. The average age is older, 72 years old. Without invasion, its prognosis is well like ductal carcinoma in situ. For non-invasive SPC, surgical complete resection is recommended. But about invasive SPC like this case, some reports said the prognosis is well, but doesn't concern about recommended additional therapy.

A case of a complete response achieved with fulvestrant following PTX/PV in HR-positive and HER2-negative breast cancer with advanced multiple liver metastasis.

Many cases have reported that paclitaxel and bevasizumab chemotherapy (PTX /BV) has high efficacy and long-term benefit in advanced and metastatic breast cancer.

Some patients have trouble to keep receiving long-term chemotherapy because of the side effects such as myelosuppression or peripheral neuropathy.

We experienced a case of a complete response achieved with fulvestrant following PTX/PV in HR-positive and HER2-negative breast cancer with advanced multiple liver metastasis.

A 51-year-old woman had marked hepatic dysfunction with multiple liver metastasis while receiving endocrine therapy (TAM+LH-RHagonist) after mastectomy and adjuvant chemotherapy.

She had a partial response within five cycles of PTX/BV and this response was maintained up to twelve cycles with improvement of liver function and tumor marker.

She refused the chemotherapy because of peripheral neuropathy and changed to fulvestrant as maintenance therapy.

In one year she achieved a complete response by imaging findings of CT scan.

Fulvestrant may be a useful agent of a maintenance therapy after gaining of a response to chemotherapy.

A case where the  $16\alpha$ - $^{18}\text{F}$ -fluoro- $17\beta$ -estradiol (FES) positron emission tomography (PET) showed change of estrogen receptor (ER) status and metabolic activity of the metastases in a patients with breast cancer and fulvestrant (FUL).

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As a non-invasive tool for examining ER for malignant lesions, FES-PET has been developed. It is reported that FES-PET can predict efficacy of hormonal therapy and estimate the ER status during hormonal therapy, with information by concurrent 2-deoxy-2- $^{18}\text{F}$ -fluoro-D-glucose (FDG) PET. We applied FES-PET and FDG-PET on a patient before and after 1 month FUL administration, who had had ER positive primary breast cancer but developed metastatic lesions after 5 year anastrozole therapy. The patient was a 78 year old woman who had had breast cancer and developed lymph node metastases in bilateral lung hilum, bilateral supraclavicular area and mediastinum, all of which showed uptake of FES and FDG. On a lymph node biopsy, the node contained ER positive breast cancer cells. After 1 month FUL administration, FDG-PET revealed much less accumulation in supraclavicular nodes, less accumulation in hilar and many mediastinal nodes, and more accumulation in some mediastinal nodes. FES-PET revealed no accumulation in all nodes. On the FDG-PET results, majority of the metastases showed less metabolic activity. Therefore, FUL had been administered. On the FES-PET results, minority of the metastases with more metabolic activity also showed no ER expression, which seemed to be induced by FUL as a blocker of the binding between ER and FES or as a selective estrogen receptor down-regulator. If FDG-PET reveals progressive metastases afterwards, they are regarded to express few ER and less respond to hormonal therapy. In such a situation, conversion to chemotherapy or additional everolimus might be a better choice. With concurrent FDG-PET, FES-PET can provide valuable and meticulous information for the treatment of ER positive metastases of breast cancer.

Eight patients with liver metastasis from breast cancer who survived for 10 years after diagnosis

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In the previous century, the results of treatment for liver metastasis from breast cancer were extremely unfavorable, and even the 5-year survival rate was low. Since the beginning of the present century, drug therapy has been developed in accordance with subtype-based disease type classification, markedly improving the prognosis of patients with metastatic breast cancer (MBC) and prolonging survival by about 5 years, excluding some disease types (Triple Negative). Currently, the number of patients in kan norimichi clinic achieving a 5-year survival after liver metastasis exceeds 30. In this study, we report 8 patients who survived for 10 years or longer after a diagnosis of liver metastasis was made, and review factors involved in the prolongation of survival.

#### [Case]

All subjects were female. Ages at the diagnosis of liver metastasis were 50 to 59 years in 5 patients, 40 to 49 years in 1, 60 to 69 years in 1, and 70 to 79 years in 1. Six patients were positive for hormone receptors. Five patients, including 2 who were negative for hormone receptors, were positive for Her2. Chemotherapy, subtype-based endocrine therapy, and molecule-targeting therapy were performed. However, all subjects underwent hepatectomy or hepatic arterial injection adoptive immunotherapy (OK-AIT): hepatectomy (6 patients), OK-AIT (5), and both (2). In addition, metastases to other sites were detected in 2 of 6 patients with liver metastasis as the initial relapse. The subjects included 2 with secondary liver metastasis following metastases to other sites. The sites of metastatic foci at the start of liver metastasis treatment consisted of bones in 4 patients, the pleura (cancerous pleural effusion) in 2, ovary in 1, peritoneum in 1, and thoracic wall in 1.

#### [Discussion]

This report does not always emphasize that topical liver therapy is necessary for achieving long-term survival. The results may have been associated with "time-related bias" based on our experience in 2005, when treatment was started for our patients. Considering the long-term control of extrahepatic metastasis in 4 patients, systemic pharmaceutical therapy is basically important. The presence of liver metastasis in metastatic foci, as the initial relapse, is significantly disadvantageous for post-relapse survival, but we emphasize that health care professionals should never give up.