extension. Furthermore, total radiation doses were reduced in some patients on the basis of irradiated normal tissue volume, and electron beam boost radiotherapy was delivered as a single anterior beam to the residual primary tumor after an initial 60 Gy was delivered.

Treatment evaluation

All patients underwent serial clinical examinations to evaluate their tumor response and acute toxic reactions. Primary tumor response was assessed by physical examination and CT. Complete response (CR) was defined as complete clinical and radiological disappearance of the tumor. No pathological measures were taken to confirm CR. Partial response (PR) was defined by a minimum 50% reduction in the product of the longest perpendicular diameters of the most easily measurable or largest tumor mass within the irradiation field. Systemic PR also required absence of growth in the other lesions and no development of new lesions for at least 28 consecutive days. Stable disease (SD) was characterized as reduction of <50% or progression of <25%. PD was characterized as progression of >25%. Local control was defined as tumor control within the field of radiation.

Acute and subacute toxicities were assessed weekly and graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). In patients treated before 2004, toxicities were initially assessed by CTCAE v2.0 followed by reassessment with v3.0. All patients' hematological profiles (including blood count, serum creatinine, and liver enzyme tests) were checked at least once in every 2 weeks during chemoradiotherapy and once in every 4 weeks after chemoradiotherapy. Late treatment-related toxicities were graded according to the Radiation Therapy Oncology Group/European Organization of Research and Treatment of Cancer's Late Effect Normal Tissue scores. Four weeks after completion of treatment, evaluations including physical examination and CT scans were performed; thereafter, identical re-evaluations were scheduled once in every 6 months.

Statistical analysis of local control rate and survival rate was performed using the Kaplan–Meier method.

Results

Patients

Between February 1998 and June 2010, 39 patients with unresectable breast tumors were treated with chemoradiotherapy at our institutes (Table 1). The median age of patients was 57 years (range 27–88 years). Menopausal status was premenopausal in 13 cases and postmenopausal in 26 cases. Tumor pathology included invasive ductal carcinoma ($n = 37$), invasive lobular carcinoma ($n = 1$), and mucinous carcinoma ($n = 1$). Clinical stages included stage IIIB ($n = 15$), stage IIIC ($n = 3$), and stage IV ($n = 21$). Tumor–node–metastasis (TNM) classifications as per the International Union Against Cancer are presented in Table 2. Symptoms accompanying breast tumors were pain ($n = 6$, 15%), discharge ($n = 31$, 79%), bleeding ($n = 24$, 62%), necrotic odor ($n = 27$, 69%), and breast tumor more than 5 cm ($n = 28$, 90%). Twenty-one cases had received previous systemic therapies, whereas 18 cases had not (Table 3). Previous treatment regimens included anthracyclines ($n = 17$), taxanes ($n = 12$), 5-fluorouracil (5FU) + prodrugs ($n = 2$), endocrine therapy ($n = 7$), and trastuzumab ($n = 1$). The reasons given for absence of previous systemic therapy were socioeconomic factors ($n = 12$), patient refusal ($n = 3$), old age ($n = 2$), poor general condition for cytotoxic therapy ($n = 1$), and copious bleeding from the primary tumor ($n = 1$).

Chemoradiotherapy

Radiation doses ranged from 56 Gy/28 fractions (Fr) to 69 Gy/33 Fr, with a median dose of 60 Gy/30 Fr. Dose for the whole breast ranged from 56 Gy/28 Fr to 60 Gy/30 Fr, and tumor boost was administered in 9 cases ($\leq$9 Gy/3 Fr). In 1 case with symptomatic supraclavicular lymph nodes metastasis, a boost of 10 Gy/5 Fr was administered in addition to a radiation dose of 50 Gy/25 Fr to the supraclavicular region.

The concurrent chemotherapies were either biweekly or weekly DTX ($n = 12$), weekly DTX + 5′DFUR ($n = 1$), weekly PTX + 5′DFUR ($n = 13$), weekly paclitaxel ($n = 1$), weekly PTX + CAP ($n = 1$), and CAP ($n = 11$) (Table 4). The reason for using DTX instead of PTX in weekly PTX + 5′DFUR regimen was that the patient had used paclitaxel and had drug resistance to paclitaxel. The reason for using PTX instead of DTX in weekly DTX + CAP regimen was the same as above. The dosage of CAP was reduced in 2 cases because of concurrent PTX administration and poor performance related to old age, respectively.

Adverse effects

Treatment toxicities are presented in Table 5. Grade 3 hematological toxicities were observed with regard to lymphocytes ($n = 13$, 33%), platelets ($n = 3$, 8%), neutrophils ($n = 1$, 3%), and hemoglobin ($n = 1$, 3%). Greater than grade 3 chemoradiation dermatitis and chemoradiation pneumonitis was observed in 9 (23%) cases and 2 (5%) cases. The latter proved fatal in 1 patient who was

Table 1 Patient characteristics

No. of patients with T4 breast tumors	39
Age (years)	
Range	27–88
Median	57
Menopausal status	
Pre	13
Post	26
Pathology	
Invasive ductal carcinoma	37
Invasive lobular carcinoma	1
Mucinous carcinoma	1
Stage	
IIIB	15
IIIC	3
IV	21
Hormone states	
ER positive	21
PgR positive	15
HER2 states	
Positive	7
Unknown	15

ER estrogen receptor, *PgR* progesterone receptor, *HER2* HER2 protein

Table 2 TNM classification

	N0	N1	N2	N3	Total
T4a	0	2 (2)	2 (1)	1	5 (3)
T4b	4 (1)	5 (3)	9 (6)	2 (1)	20 (11)
T4c	0	8 (3)	1	5 (4)	14 (7)
Total	4 (1)	15 (8)	12 (7)	8 (5)	39 (21)

Values in parenthesis represent the number of M1 cases

Table 3 Previous treatment

	M0	M1	Total
Previous treatment			
No	8	10	18 (46%)
Yes	10	11	21 (54%)
Anthracycline regimen	8	9	17
Taxanes	7	5	12
5FU and prodrugs	1	1	2
Endocrine therapy	3	4	7
Trastuzumab	0	1	1
Total	18	21	39

receiving biweekly DTX along with radiation to the primary tumor as well as numerous satellite lesions surrounding the primary tumor.

Table 4 Concurrent chemotherapy for T4 breast tumor

	M0	M1	Total
DTX	3	9	12
PTX	1	0	1
PTX + 5′DFUR	7	6	13
DTX + 5′DFUR	0	1	1
DTX + CAP	0	1	1
CAP	6	5	11

DTX docetaxel, *PTX* paclitaxel, *5′DFUR* doxifluridine, *CAP* capecitabine

Table 5 Acute adverse effects

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukocytes	3	5			
Neutrophils	3	3	1		
Lymphopenia	2	11	13		
Hemoglobin	7	5	1		
Platelets	1	1	3		
Chemoradiation dermatitis	8	22	9		
Hand–foot syndrome	1				
Alopecia	5	6			
Chemoradiation pneumonitis			1		1
Nausea	3				

Response and prognosis

Local response to treatment according to irradiated tumor site is presented in Table 6. Sixteen primary tumors (41%) exhibited CR, and 21 (53%) exhibited PR. The CR rate at the irradiated site was 62% with DTX, 40% with paclitaxel, and 17% with CAP. Symptomatic improvement was recognized in all patients. Bleeding from tumor disappeared in all 24 patients. Discharge and necrotic odor was further improved in most of all patients, and ulceration of breast disappeared in 77% (24/31) of the patients. The systemic treatment response, including that at the nonirradiated sites, 1 month after completion of radiotherapy was CR ($n = 7$, 18%), PR ($n = 27$, 69%), SD ($n = 3$, 8%), and PD ($n = 2$, 5%). Systemic CR rate was 8% with DTX, 33% with PTX, and 17% with CAP. One of the T4c cases who achieved CR is shown in Fig. 1.

The median follow-up period was 20 months (range 3–96 months). All patients were treated with chemotherapy and/or endocrine therapy after completion of chemoradiotherapy. Twenty-nine patients showed relapse, and 19 died

Table 6 Local control

	M0	M1	Total
CR	6	10	16 (41%)
PR	12	9	21 (53%)
SD	0	2	2 (6%)
PD	0	0	0
Total	18	21	39 (100%)

Follow-up time: 3–77 months, median follow-up time: 22 months

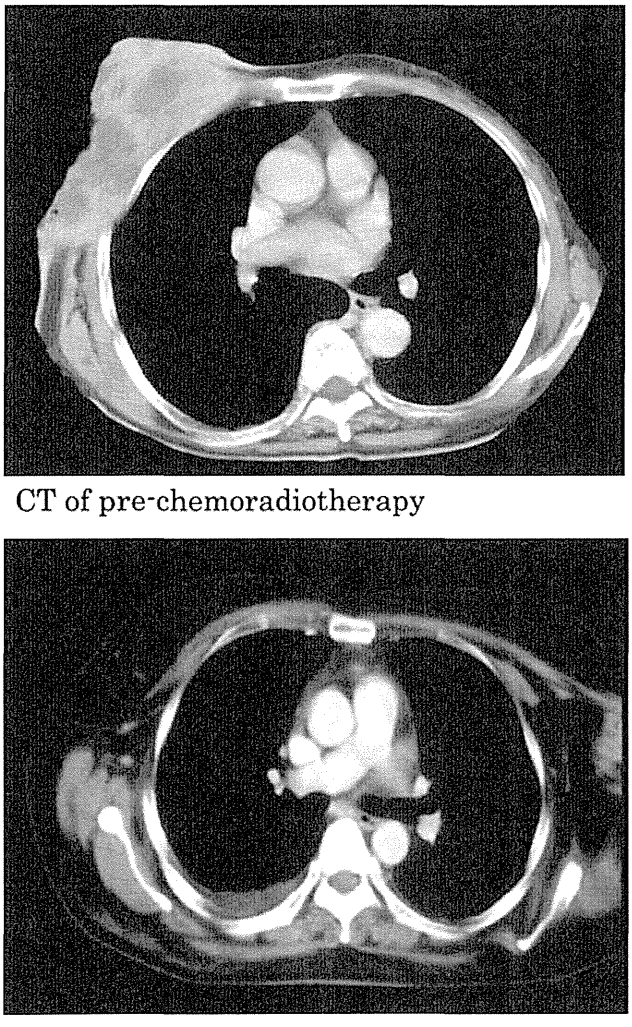

Fig. 1 Forty-three-year-old female T4cN2aM1 (bone). Rt. breast and axillary LNs irradiated 62 Gy + DTX 40 mg/m^2/biweekly. Refused other treatment for socioeconomical reason. Died after 2.3 years with systemic disease

from progressive breast cancer. Infield residual tumors or recurrence was observed in 11 patients, although only 3 exhibited symptomatic relapse. The local control rate at 2 years was 73.6% overall, 50.0% for stage T4a, 78.3% for stage T4b, and 77.1% for stage T4c tumors. The overall survival rate at 2 years was 65.9% (87.2% for stage III and 67.5% for stage IV tumors).

Discussion

We treated 39 cases of T4 breast cancer over the previous 12 years 4 months, i.e., approximately 1 case per 4 months, which is not a negligible number. Most were referred to our institutes because the surgeons involved considered these cases as unsuitable for further conventional treatment at their clinic.

Patients with unresectable primary T4 breast tumors are usually treated with systemic therapies. If these prove sufficiently effective, there is no need to consider local therapies. Response rates to chemotherapy plus molecular targeting agent therapy have improved considerably in recent times, although pathologic CR rate still remains at around 20–30% with those regimens [7, 8]. Therefore, other possibilities are considered to be required. Symptoms accompanying advanced breast tumors, such as pain, discharge, bleeding, necrotic odor, and large size, reduce the quality of life of patients. Therefore, primary tumor control and symptom relief should be given importance equivalent to that of survival.

Previously, photon radiotherapy has been attempted to achieve local control of T4 tumors; however, it proved ineffective in terms of achieving local control without the aid of other therapies [9, 10]. Several techniques have been used to improve radiation response, including enhancement of dose distribution, particle beam therapy, and combination with drugs, which include radiosensitizers for tumor tissue and radioprotectants for normal tissue. However, because these drugs are not sufficiently effective if used alone, chemotherapy is concurrently used as the radiosensitizer [4–6].

Previously, 5FU and its prodrugs (mitomycin C and pepleomycin) were used. Examples of more recently used radiosensitizers include: monotherapy with temozolomide (for glioblastoma) or combination therapy with platinum, 5FU, and taxanes (for head and neck and esophageal cancer); platinum and taxanes or etoposide (for lung cancer); gemcitabine and TS-1 (for pancreatic cancer); and cisplatin (for uterine cervical cancer). Chemoradiotherapy is a standard technique of local treatment for advanced tumors, and is also used as a part of therapy for metastatic disease [2, 3].

Usually, chemotherapy, endocrine therapy, molecular targeting therapy supported by surgery, and postoperative radiotherapy are performed sequentially during general treatment of breast cancer. Although this is the safest way, combination therapy such as chemoradiotherapy is a further option to improve patient response [4–6].

Taxanes are antimetabolites having a strong radiosensitizing effect and are good chemoradiotherapeutic agents [11, 12]. The results of our study on the use of taxanes as chemoradiotherapeutic agents for breast cancer indicated that the dosage of taxanes must be reduced to avoid lung, skin, and hematological toxicities [13].

We initially used DTX at a low dose to observe radiosensitizing effect in normal tissue. DTX is an antimicrotubule agent that has possible additive or synergistic benefits [14]. We treated 2 cases biweekly and 11 cases weekly with this treatment regimen; biweekly therapy was initiated after the publication of reports documenting less adverse effects of this protocol. However, death due to toxic effects of biweekly therapy on the lung occurred in 1 patient, and the regimen was subsequently replaced by weekly therapy [13].

Ten of 13 cases (77%) treated with DTX showed grade 3 lymphopenia and 1 showed grade 3 neutropenia, but there was little evidence of other myelosuppression with this treatment regimen. Among patients who received weekly therapy, grade 3 pneumonitis occurred in 1. The treatment-related death due to lung toxicity may have been caused by *Pneumocystis carinii* pneumonia induced by grade 3 lymphopenia and high lung doses of electron one-portal irradiation. On autopsy of this case, extensive lymphocyte infiltration at irradiated area was noted. Careful attention must be paid to immunosuppressive events in cases with concurrent DTX use [15, 16]. Dermatitis was below grade 2 in all cases. Local CR rate in DTX cases was 62% (8/13). There was no local recurrence among the CR cases, whereas there were 2 cases of recurrence among the PR cases. This was the highest CR rate in this study.

PTX was administered in 15 cases as follows: PTX + 5′DFUR in 13, PTX alone in 1, and PTX + CAP in 1. Among these, pneumonitis did not occur in any patient. Grade 3 lymphopenia occurred in 3 patients; however, no other grade 3 toxicities were reported. The local CR rate was 40% (6/15). There was no local recurrence among CR cases, but there were 3 among PR cases.

CAP is easily administered orally, and is generally administered in resistant cases after treatment with anthracyclines and taxanes. Because it metabolizes to 5FU in tumor tissue, little systemic toxicity is noted. CAP has a radiosensitive effect also [17–19]. Chemoradiotherapy with CAP at a lower dosage than that administered conventionally is widely used for digestive system malignancies; this reduced dosage is on account of gastrointestinal toxicity, which is irrelevant in breast irradiation. The CAP

Table 7 Chemoradiotherapy for advanced breast cancer

Trial	Number	Chemo	Administration	Total dose (Gy)	Response	Toxicity	Treatment result
Bellon et al. [24]	44	DTX PTX				Grade 3 dermatitis 20%	
Formenti et al. [25]	44	PTX		45 Gy	RR 16%, operable case pCR 91%		
Kao et al. [26]	23	PTX VNB	Continuous infusion Intravenous	60–70 Gy	pCR 48%	Grade 3 dermatitis 50% Grade 3–4 neutropenia 19%	4-Year LCR 83%, 4-year OS 56%
Karasawa et al. [13]	35	DTX	40 mg/m^2 bw or 20 mg/m^2 ew	54–69 Gy (median 60 Gy)	CR 68%	Dermatitis increased but acceptable	
Koukourakis et al. [27]	22	5′DFUR DTX Trastuzumab	25 mg/m^2 ew 40 mg/m^2 ew 4 mg/kg bw	Conc Amifostine Acc Hyperfrac	CR 71%	Increase but acceptable	
Genet et al. [28]	66	EPI + CPA + VDS CDDP + 5FU MTX, CEF	50 + 350 + 3 10 + 500 6 days 1500, (500, 500, 75)	65 Gy bid	CR 88%	Grade 3–4 neutropenia 50%, thrombosis 8	Median DFS 28 months, median OS 55.5 months
Shanta et al. [29]	1117	CMF CAF	6000, 600, 40 600, 600, 75	40 Gy		Grade 3 dermatitis common	5-year OS 75.6%, 5-year DFS 64.5%

DTX docetaxel, *PTX* paclitaxel, *5′DFUR* doxifluridine, *VNB* vinorelbine, *EPI* epirubicin, *CPA* cyclophosphamide, *VDS* vindesine, *CDDP* cisplatin, *MTX* methotrexate, *CEF* CPA + EPI + 5FU, *ew* weekly, *bw* biweekly, *Conc* concurrent, *Acc Hyperfract* accelerated hyperfractionated radiotherapy, *Bt* mastectomy, *LCR* local control rate, *OS* overall survival, *DFS* disease-free survival

specific adverse effects of hand–foot syndrome are not related to adverse radiation effects, so we surmised that conventional dosages of CAP would be a suitable regimen for breast irradiation. CAP was used in 12 patients; 11 were administrated a conventional dose, and 1 was administered a reduced dose. The latter patient was 82 years old with history of cerebral infarction; moreover, she was bedridden. Of the former 11, one patient was administered CAP in combination with PTX. Adverse grade 3 hematological toxicities included lymphopenia ($n = 1$) and lowered hemoglobin ($n = 1$) in CAP regimen. Grade 3 dermatitis was noted in 1 case, and no other grade 3 toxicities were observed in CAP regimen. Local control rate with CAP was 17% (2/12). There was no local recurrence among the CR cases and 6 local recurrences among the PR cases. This may be due to tumor heterogeneity, such as tumor size or disease extension. However, the CR rate with CAP was the lowest in our study.

Systemic CR was noted in 7 stage IIIB cases: 1 with DTX, 4 with PTX, and 2 with CAP administration. The CR rate was 8% with DTX, 33% with PTX, and 17% with CAP. The low systemic CR rate in patients treated with DTX is probably related to the percentage of stage III patients in that arm. That percent of stage III patients of each regimen was 23% with DTX, 50% with paclitaxel, and 58% with CAP.

Local control rate was better with DTX, although adverse effects were more severe than with other regimens. The bias of tumor volume and extension varied, making comparison of CR rates between treatment regimens problematic. Pneumonitis occurred only with DTX administration, although one case of adverse effects on the lung was recorded during the early stages of the trial.

Local recurrence was noted in 11 cases, although only 3 cases treated with CAP were symptomatic. The other 8 cases were diagnosed as asymptomatic local recurrence by imaging modalities.

The results of our study indicate that careful administration of taxanes, especially DTX, must be considered as a treatment option for unresectable T4 breast tumors. In the literature concerning resectable advanced breast tumors, there are many reports of surgery plus postoperative irradiation combined with sequential systemic chemotherapy [20–23]; however, only a few reports are available on systemic chemoradiotherapy for unresectable breast tumors (Table 7 [13, 24–29]).

In conclusion, we believe that a 6-week course of chemoradiotherapy as a part of systemic treatment for unresectable breast tumors represents a feasible option, although the dose applied to the lung should be carefully evaluated to avoid fatal lung toxicities.

Written informed consent was obtained from all patients.

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

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Breast Cancer
DOI 10.1007/s12282-013-0448-4

CASE REPORT

Tumor lysis syndrome following trastuzumab for breast cancer: a case report and review of the literature

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Received: 1 October 2012 / Accepted: 23 January 2013

Abstract Tumor lysis syndrome, a complication of anticancer chemotherapy, results from rapid lysis of malignant cells. We report tumor lysis syndrome in a patient treated with trastuzumab for metastatic breast carcinoma. A 69-year-old woman was diagnosed with multiple liver metastases 1 month after mastectomy. As her liver functions had deteriorated, chemotherapeutic agents were contraindicated and she was treated with trastuzumab alone. On day 6 of the first course of trastuzumab, she developed tumor lysis syndrome. As her liver functions showed deterioration due to multiple hepatic metastases, hemodialysis was contraindicated. Acute renal failure worsened and she died 11 days after the administration of trastuzumab.

Keywords Tumor lysis syndrome · Solid tumor · Breast cancer · Trastuzumab · Molecular targeting drug

Introduction

Tumor lysis syndrome (TLS), a complication of anticancer chemotherapy, results from rapid lysis of malignant cells. TLS has been described as occurring much more frequently in hematological malignancies than solid tumors, in which this complication is also rare. We report TLS in a patient treated with trastuzumab for metastatic breast carcinoma. To our knowledge, this is the first case report of TLS following trastuzumab for breast cancer.

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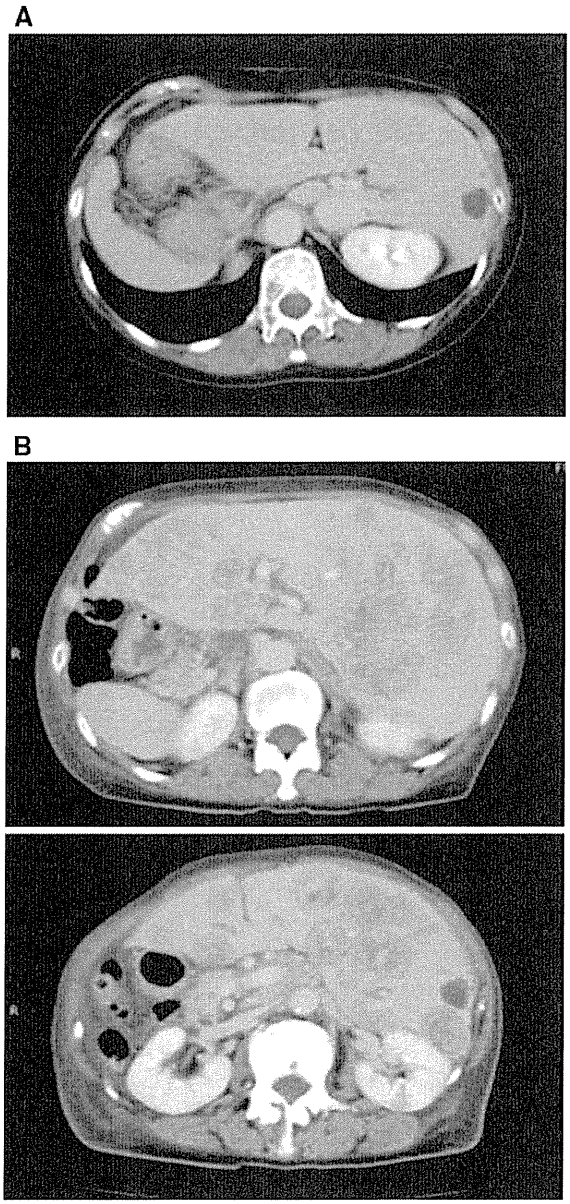
Case report

A 69-year-old postmenopausal woman with situs inversus totalis came to our hospital for evaluation of a right breast lump. We diagnosed right breast cancer with axillary lymph node metastasis (invasive ductal carcinoma, triple-positive T2N1M0 stage IIB). She received 4 cycles of FEC (i.e., 500 mg/m^2 of 5-FU, 75 mg/m^2 of epirubicin, 500 mg/m^2 of cyclophosphamide) and 4 cycles of docetaxel (75 mg/m^2) as neoadjuvant chemotherapy (NAC). During NAC the tumor shrank markedly. Upon completion of NAC, magnetic resonance imaging (MRI) showed a complete clinical response. No distant metastases were detected either before or after NAC (Fig. 1a). We performed a right mastectomy and axillary lymph node dissection. The tumor showed a pathological complete response except for metastasis involving 11 of the 23 lymph nodes resected.

One month after the operation, she experienced appetite loss. Ultrasonography and computed tomography showed multiple liver metastases (Fig. 1b) and tumor markers (CEA, CA15-3) were elevated (Fig. 2). As her liver functions had deteriorated, chemotherapeutic agents were contraindicated. The only agents reportedly which are not metabolized in the liver or kidneys are biological agents such as trastuzumab. After discussing the treatment options with the patient and her family, we decided to administer trastuzumab. Laboratory results before treatment indicated decreased liver function, but there were no complications suggestive of TLS or renal failure (Table 1). On day 6 of the first course of trastuzumab, a grade 4 cardiac arrhythmia developed. Blood tests showed hyperkalemia (8.1 mmol/l), hyperuricemia (22.2 mg/dl), high lactate dehydrogenase (LDH) (2297 IU/l), grade 2 hypocalcemia (7.4 mg/dl), and hyperphosphatemia (6.4 mg/dl), indicating a diagnosis of TLS. Despite hydration, calcium

Published online: 19 February 2013



◀ **Fig. 1** **a** No liver metastasis was detected at the end of NAC. The liver was oriented in a mirror image of its usual anatomical position because of situs inversus totalis. **b** Computed tomography showed multiple liver metastasis

gluconate infusion, and urine alkalization, electrolyte abnormalities and renal function did not improve. Her liver functions deteriorated markedly as a result of multiple hepatic metastases, such that hemodialysis was contraindicated. Recombinant urate oxidase (rasburicase) was also considered for the treatment of hyperuricemia. However, only preventive use of rasburicase is covered by insurance in our country owing to the high cost of this drug. Moreover, the prospects for recovery from hyperuricemia were poor, and rasburicase was thus not administered. We treated hyperkalemia with glucose and insulin infusion, and renal failure with furosemide infusion. Acute renal failure worsened and she died 11 days after starting trastuzumab.

Discussion

Tumor lysis syndrome has been described as occurring much more frequently in hematological malignancies than in solid tumors, in which this complication is also rare [1]. Risk factors for TLS include a high tumor cell proliferation rate, large tumor burden, tumor chemo-sensitivity, a high LDH level, high uric acid level, and pre-existing renal insufficiency [2]. With recognition of the high risk of TLS and taking precautions such as hydration, or, at least, frequent laboratory evaluations during and after treatment, this fatal condition might have been avoided.

TLS with solid tumors has been reported in lung cancer, liver cancer, breast cancer, gastric cancer, colorectal cancer, seminoma, medulloblastoma, and sarcoma [3–35].

Our literature search for "TLS" with "solid tumor", limited to adult cases only, yielded 38 case reports. Various

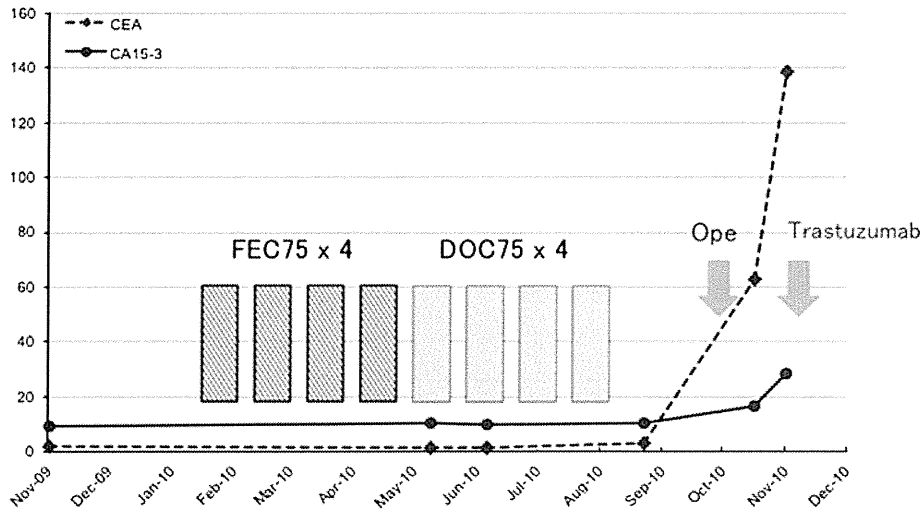


Fig. 2 Serum tumor marker levels with clinical course

Table 1 Laboratory values before and after trastuzumab

Laboratory	Before treatment	7 days after trastuzumab
ALP (IU/l)	1,526	2,019
AST (IU/l)	658	620
ALT (IU/l)	201	243
LDH (IU/l)	931	2,297
BUN (mg/dl)	23	108
Creatinine (mg/dl)	0.64	7.06
Uric acid (mg/dl)		22.2
Na (mmol/l)	137	130
K (mmol/l)	4.3	8.1
Ca (mg/dl)	9.5	7.4
P (mg/dl)		6.4

ALP alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BUN* blood urea nitrogen

organs have been reported as the primary site, including 7 lung cancers (18.4 %), 5 breast cancers (13.1 %), 5 hepatocellular carcinomas (HCC) (13.2 %), and tumors of several other organs (Table 2). It is noteworthy that 70 % of cases in total had liver metastasis. Furthermore, more than 85 %, of TLS cases had hepatic involvement, including both HCC, and liver metastasis patients. The liver is one of the largest organs, and assessment of hepatic lesions is important for assessing the risk of TLS. Nearly 70 % of TLS cases are reportedly due to chemotherapy, though cases with spontaneous TLS (STLS) [8, 12, 16, 24, 31] and TLS caused by hormonal or radiation therapy [14, 15] have also been reported. Among cases with TLS due to drug therapy, almost 90 % had an onset within 2.0 days (median) after administration of the first cycle of treatment. In addition to the risk factors mentioned above, patients with solid tumors should be assessed for other risk factors such as bulky tumor mass with metastatic presentation especially in the liver. In the present case, the tumor characteristics of high sensitivity to chemotherapy and high volume of liver metastasis were risk factors for TLS.

Our search for "TLS" with "breast cancer" yielded 11 cases (Table 3) [3, 14–16, 36–41]. Histologies of these breast cancers were mainly invasive ductal carcinomas and hormone status was usually unclear. All cases had distant metastasis and eight of the 11 (72.7 %) had liver metastasis. Only five cases recovered from TLS, i.e., more than half had a fatal course. While nearly all had TLS induced by chemotherapy, there were also cases with TLS triggered by hormonal and radiation therapy [14, 15, 41]. In two cases, several drugs had been administered prior to the occurrence of TLS [3], suggesting different sensitivities to breast cancer drugs.

To our knowledge, this is the first case report of TLS following trastuzumab administration for breast cancer.

Table 2 Reported cases of TLS with solid tumors

	Number (*n*)
Age (years)[a]	61.0 (17–82)
Sex	
Male	23
Female	15
Primary site	
Lung	7
Breast	5
Liver	5
Stomach	3
Colon	2
Ovary	2
Skin	2
Others	12
Distant metastasis	
Yes	29
Metastasis site	
Liver	21
Bone	11
Lung	12
Brain	2
Others	10
No	2
NA	7
Treatment for metastatic disease	
Drug therapy	29
Chemotherapy	26
Molecular targeting drug	3
Other drugs[b]	3
Radiation	1
None	8
Number of cycles	
1st cycle	27
2nd cycle	1
NA	1
Time to onset of TLS from treatment (days)[a,c]	2.0 (1–16)

Data are reported as numbers unless otherwise indicated

NA not available

[a] Data are median (range)

[b] Aromatase inhibitor, zoledronic acid, hydrocortisone

[c] 24 h = 1 day

There were only three patients with TLS associated with molecular targeting therapy among the 38 aforementioned cases [13, 17, 26]. Sorafenib for HCC, sunitinib for renal carcinoma, and imatinib for gastrointestinal stromal tumors were administered. There were no differences in the onset and course of TLS from those of cases receiving other anticancer drugs. We speculate that the recently developed

highly effective chemotherapeutic agents, including molecular targeting drugs for solid tumors, are associated with higher risks of massive tumor necrosis and the associated complications, including TLS. These risks must be weighed against the therapeutic benefits. In addition, the mortality rate associated with TLS in solid tumors is reportedly higher than that with hematological malignancies [1]. Thus, it is crucial to evaluate individual risk appropriately and implement preventive therapy. Early recognition and aggressive therapy can prevent mortality when TLS occurs. While TLS with solid tumors is rare, we should always keep this possibility in mind, and high-risk patients must be identified and the risk of TLS appropriately estimated.

Acknowledgments We thank the patient, her family, and the personnel involved in the treatment of this case.

Conflict of interest None.

Table 3 Eleven cases of TLS with breast cancer

Sex	Age (years)	Histology	ER	PR	HER2/neu	Distant metastasis	Treatment after diagnosis of distant metastasis	Onset of TLS	Outcome of TLS
F	47	NA	+	−	−	Lung, bone, kidney	TXT → RT → FEC	1st–2nd day	Recovered
F	44	NA	+	+	+	Bone, liver	TAM + TR → TXT → VNR → GEM + CDDP	1st–2nd day	Recovered
F	42	IDC	NA	NA	NA	Liver	CAP	1st–11 h after	Deceased
F	61	IDC	+	+	NA	Pleura	LET	1st–2nd day	Recovered
M	73	IDC	NA	NA	NA	Lung, liver, bone	RT	1st–3rd day	Deceased
F	56	NA	NA	NA	NA	Liver	TXL	1st–during infusion	Deceased
F	62	Inflammatory breast cancer, lobular carcinoma	NA	NA	NA	Bone, lung, liver, bone marrow	None (STLS) → recurrence with VMT	UN	Deceased
F	31	IDC	+	NA	NA	Liver	MIT	1st–5th day	Recovered
F	57	IDC	−	−	NA	Lung, liver	CMF	1st–2nd day	Deceased
F	53	Adenocarcinoma	−	−	NA	Chest wall, liver	CAF	1st–18 h	Deceased
F	94	IDC	NA	NA	NA	Bone	TAM	1st–1 week	Recovered

NA not available, *IDC* invasive ductal carcinoma, *ER* estrogen receptor, *PR* progesterone receptor, *TXT* docetaxel, *RT* radiotherapy, *FEC* 5-FU + cyclophosphamide + epirubicin, *TAM* tamoxifen, *TR* trastuzumab, *VNR* vinorelbine, *GEM* gemcitabine, *CDDP* cisplatin, *CAP* capecitabine, *LET* letrozole, *TXL* paclitaxel, *STLS* spontaneous tumor lysis syndrome, *VMT* vinblastine + methotrexate + thiotepa, *MIT* mitoxantrone, *CMF* cyclophosphamide + methotrexate + 5-FU, *CAF* cyclophosphamide + doxorubicin + 5-FU

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