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CLINICAL TRIAL

Comparison among different classification systems regarding the pathological response of preoperative chemotherapy in relation to the long-term outcome

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Abstract Neoadjuvant chemotherapy (NAC) is increasingly used for operable disease. However there are several pathological response classification systems and the correlation between the pathological response to NAC according to each system and the patient outcome is still under debate. From 1998 to 2006, 370 primary breast cancer patients underwent curative surgical treatment after NAC containing both anthracycline and taxane at the National Cancer Center Hospital. We retrospectively evaluated the clinical and pathological response using the cTMN, Fisher's, Chevailler's, and the Japanese Breast Cancer Society classification systems (JBCS) respectively, and analyzed the correlation between each pathological response and disease free survival (DFS). Ninety-five (26%) patients had tumor recurrence. The five-year DFS according to Fisher's system was pCR, 80% and pINV, 63%. The five-year DFS according to Chevallier's system was Grade 1, 83%, Grade 2, 85%, Grade 3, 62%, and Grade 4, 65%. The five-year DFS according to the JBSC system was Grade 3, 77%, Grade 2, 68%, Grade 1a, 68%, Grade 1b, 58%, and Grade 0, 52%. None of the pathological response systems reached a statistically significant difference. In the classification by the post-treatment number of metastatic axillary lymph nodes, the 5-year DFS was $n = 0$, 86%; $n = 1$–3, 64%; $n = 4$–9, 44%; and $n > 10$ positive: 25% ($P < .0001$). In pathologically node negative patients, there were no significant differences in the DFS among all the classification systems. All three classifications analyzed were considered inadequate as the prognostic marker of the long-term outcome after NAC and further studies are warranted to optimize the prediction.

Keywords Breast cancer · Neoadjuvant · Chemotherapy · Response · Predictor

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Introduction

Breast cancer has recently become the most common malignancy among Japanese women. Approximately 40,000 women are annually affected and breast cancer mortality has been increasing. National efforts to establish an early detection system by screening mammography has begun, but many of the primary cases still present with a palpable mass in the breast.

Neoadjuvant chemotherapy (NAC) has been accepted as one of the standards of care not only for locally advanced breast cancer but also for primary operable breast cancer. The disease free survival (DFS) and overall survival (OS) of patients treated with NAC is at least equivalent to those treated with post-operative adjuvant chemotherapy and the chance of breast conservation increases in patients with larger tumors [1, 2]. Although the benefit of the addition of taxane to anthracycline in the preoperative setting in terms of long-term outcome remains controversial, regimens that

combine both anthracycline and taxane, either sequentially or concomitantly, are widely used.

Prognostic factors after primary chemotherapy include the clinical and pathological response to primary chemotherapy, the cTNM stage, and axillary lymph-node status after chemotherapy. "Pathological complete response (pCR)" correlates with an improved DFS and OS and has often been used as the surrogate primary endpoint for NAC. However, the classification systems for pathological response vary among studies and the system that best reflects the long-term outcome remains unidentified. Thus in this study, we applied various pathological response systems in the published literature to the same patient cohort treated with NAC including anthracycline and taxane to compare their usefulness in the prediction of the long-term outcome after NAC.

Patients and methods

Patients and treatments

All breast cancer patients treated with NAC containing both anthracycline and taxane between May 1998 and October 2006 at the National Cancer Center Hospital were extracted from the surgical database to be included in this retrospective study. NAC was indicated in patients with clinical stage II or III primary breast cancer with tumors larger than 3 cm. Core needle biopsy was performed before NAC to obtain a pathological diagnosis. The NAC regimens included (1) four cycles of doxorubicin (DOX, 50 mg/m^2) and docetaxel (DOC, 60 mg/m^2) (AT) followed by additional adjuvant treatment with two cycles of AT or four cycles of iv CMF (cyclophosphamide, methotrexate and 5FU), (2) four cycles of fluorouracil (500 mg/m^2)/epirubicin (100 mg/m^2)/cyclophosphamide (500 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) (FECT), (3) four cycles of doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) (ACT). After November 2002, in patients with HER2-overexpression tumors, trastsuzumab (initially 4 mg/kg and 2 mg/kg weekly) was administered with paclitaxel for 12 weeks in the ACT and FECT treated populations (ACTH and FECTH, respectively). Five years of endocrine therapy was scheduled when either the pretreatment biopsy specimen or surgical specimen post-chemotherapy were positive for the estrogen or progesterone receptor.

Evaluation of pathological factors

Pretreatment diagnosis was established by pathologists from a core needle biopsy specimen. Surgical specimens were sectioned at about 7–10 mm and the pathological response was evaluated by pathologists. The expression levels of ER (1D5, Dako Cytomation), PgR (1A6, Novocastra) and HER2 (HercepTest®, Dako Cytomation) were examined with immunohistological staining. ER and PgR were classed as positive when more than 10% of cancer cell nuclei were stained, regardless of the intensity of the staining. HER2 was scored as follows: (0): negative for cells, (1+): slightly positive in more than 10% of cancer cells, (2+): moderately positive in more than 10% of cancer cells, (3+): markedly positive in more than 10% of cancer cells. Additional fluorescent in situ hybridization (FISH) for HER2 amplification (Pathvision, Vysis) was performed and when IHC (3+) or FISH-positive (HER2/CEP17 signal ratio $\geq$ 2.0) were defined as HER2-positive.

The response criteria used in this study included Fisher's system [1], Chevalier's system [3] and the histological response criteria of the Japanese Breast Cancer Society (JBCS) [4, 5]. The key definitions of each response classification system are described in Table 1. To summarize, Fisher's system evaluated only the histological evidence of invasive disease in the primary tumor, Chevallier's system incorporated nodal status and the JBSC system measured morphological changes in of the tumor cells and the proportion of histological changes in the primary tumor. The histological effect in both the primary tumor and axillary lymph node should be separately evaluated in the JBCS system, but the standard of how to combine the effect is not mentioned. Therefore we used the pathological response in only the primary lesion in the present study.

In addition, we evaluated pretreatment clinical staging, the clinical response to preoperative chemotherapy and postoperative pathological lymph node status. The clinical response to preoperative chemotherapy was decided from the two greatest perpendicular diameters (before each chemotherapy treatment and before surgery) of tumors in the breast and axillary lymph nodes. No clinical evidence of palpable tumor in the breast and axillary lymph nodes was defined as a clinical complete response (cCR). A reduction in the total tumor size of 30% or greater was graded as clinical partial response (cPR). An increase in total tumor size of more than 20% or appearance of new suspicious ipsilateral axillary adenopathy was considered progressive disease (cPD). Tumors that did not meet the criteria for objective response and progression were considered as stable disease (cSD).

Statistical analysis

Disease free survival (DFS) was calculated from the date that NC was initiated to the date of the first relapse including loco-regional recurrence or the last visit without

Table 1 Pathological response classification systems

Classification system	Key definitions
Fisher et al. [1]	Classification based on microscopic evidence
	pCR = no histological evidence of invasive tumor cells (specimens with only noninvasive cells included)
	pINV = histological evidence of invasive disease of any extent
Chevallier et al. [3]	Classification using both microscopic and macroscopic evidence
	Grade 1 (pCR) = disappearance of all tumor on either macroscopic or microscopic assessment
	Grade 2 = presence of in situ carcinoma in the breast, no invasive tumor, no tumor in the ALNs
	Grade 3 = presence of invasive carcinoma with stromal alteration
	Grade 4 = no/few modifications of the tumor appearance
JBCS	Classification using both microscopic and macroscopic evidence in primary tumor
	Grade 0 = no therapeutic effect
	Grade 1 = <66% therapeutic effect, but >33% effect evident
	Grade 2 = subjectively >66% therapeutic effect, but <near total therapeutic effect
	Grade 3 = disappearance of all tumor on either macroscopic or microscopic assessment

pCR, pathological complete response; ALN, Axillary lymph node; pINV, pathological invasive disease; JBCS, Japanese breast cancer society

relapse. Kaplan–Meier plots and the log-rank test were used to assess the difference in survival. All comparisons were two-tailed. Cox-proportional hazards models were fitted for OS and DFS and included variables identified a priori as being associated with survival and the ALN status. Other variables not identified a priori were entered into the model one at a time and assessed for statistical significance. All pair-wise interactions were tested. The fit of the model and the proportional hazards assumption were assessed visually with residual plots. The statistical significance level (P) was taken as a measure of the strength of evidence against the null hypothesis, and $P < .05$ was considered statistically significant.

Results

Three hundred and seventy patients with operable breast cancer were included in this study. Table 2 lists the patient and tumor characteristics. The median age was 50 years (26–71) and 192 (52%) patients were over the age of 50. Clinical staging at diagnosis was IIA in 104 (28%), IIB in 114 (31%), IIIA in 75 (20%) and IIIB in 77 (21%). ER and PgR positive patients were respectively 148 (40%) and 152 (41%). 183 (49%) patients were treated with AT, 73 (20%) with ACT and 90 (24%) with FECT. Trastuzumab as administered to four patients among the ACT-treated patients (ACTH) and 20 among the FECT-treated patients. Ten percent of patients with HER2-positive breast cancer received trastuzumab in this study.

Ninety-six patients (26%) had tumor recurrence with a median follow-up of 45 months (range 4–104). Nine patients had only loco-regional recurrence without distant metastasis. Only 42 patients died within this period.

The clinical and pathological response results are shown in Table 3. The overall clinical response rate to NAC was 88% (cCR + cPR) and the cCR rate was 28%. According to Fisher's classification, pCR and pINV was 65 (18%) and 305 (82%). According to Chevallier's classification, 30 (8%) patients achieved a Grade 1 (disappearance of all

Table 2 Patient and tumor characteristics

Parameter	No. of patients (%)
Total	370
Age	
Age <50	179 (48)
Age >51	191 (52)
Pretreatment pathology	
Invasive ductal carcinoma	347 (94)
Invasive lobular carcinoma	13 (4)
Mucinous carcinoma	7 (2)
Others	3 (1)
Hormone receptors	
ER positive	148 (40)
PgR positive	152 (41)
HER2	
Positive (>2+)	132 (36)
Neoadjuvant chemotherapy	
AT	183 (49)
ACT	73 (20)
ACTH	4 (1)
FECT	90 (24)
FECTH	20 (5)
Surgery	
Partial mastectomy	136 (37)
Total mastectomy	234 (63)

Table 3 Response to neoadjuvant chemotherapy, Cox proportional hazards model for disease free survival

Parameter	No. of patients (%)	Hazard ratio (95% CI)
Fisher's classification		
pCR	65 (18)	1.00
pINV	305 (82)	1.07 (0.56–2.73)
Chevallier's classification		
Grade 1	30 (8)	1.00
Grade 2	21 (6)	1.03 (0.18–5.85)
Grade 3	172 (46)	1.00 (0.43–2.26)
Grade 4	147 (40)	1.31 (0.27–5.66)
JBCS classification		
Grade 3	34 (9)	1.00
Grade 2	102 (28)	1.39 (0.54–3.39)
Grade 1b	81 (22)	0.96 (0.36–2.32)
Grade 1a	141 (38)	0.61 (0.21–1.71)
Grade 0	12 (3)	0.50 (0.56–2.73)
Pathological lymph node status		
$n = 0$	174 (47)	1.00
$n = 1$–3	102 (28)	0.78 (0.54–1.10)
$n = 4$–9	57 (15)	1.57* (1.07–2.24)
$n > 10$	37 (10)	2.71* (1.83–3.95)
Clinical stage		
IIA	104 (28)	1.00
IIB	114 (31)	0.68 (0.45–1.01)
IIIA	75 (20)	1.23 (0.86–1.74)
IIIB	77 (21)	1.22 (0.85–1.74)
Clinical response		
CCR + cPR	324 (88)	1.00
CSD + cPD	46 (12)	1.44* (1.10–1.87)

CI, Confidence interval, * $P < .001$

tumors in either breast or lymph node) pathological response. According to the JBCS classification, there were 34 (9%) patients with Grade 3 pathological response (pathologically no residual tumor in the breast). Post-treatment pathological nodal status was negative in 174 (47%), 1–3 positive in 102 (28%), 4–9 positive in 57 (15%), and >10 positive in 37 (10%) patients, respectively. In the Cox proportional hazards model, the classification of pathological lymph node status and clinical response were identified as being independently significantly associated with patient outcomes (Table 3). Pretreatment hormone receptor status was not associated with pathological response or DFS. Inclusion of trastuzumab in NAC was associated with the pathological response in HER2-positive tumors ($P = 0.04$), but there was no statistical difference in the DFS (data not shown).

Figure 1 illustrates the Kaplan–Meier curves of the patient cohort of DFS according to each pathological response classification system (Fisher's, Chevallier's, JBCS). Among these classification systems, Fisher's tended to show a correlation with DFS, however, it did not reach a statistically significant difference ($P = .067$). The five-year DFS rates in Grade 3, Grade 2, Grade 1a, Grade 1b and Grade according to the JBCS system were 77%, 68%, 68%, 58%, and 52%, respectively ($P = .525$). According to Chevallier's system, the five-year DFS rates for Grade 1, Grade 2, Grade 3 and Grade 4 were 83%, 85%, 62% and 65%, respectively ($P = .16$).

The five-year DFS according to the number of post-treatment axillary node metastases was $n = 0$, 86%; $n = 1$–3, 64%; and $n = 4$–9, 25%. Figure 2 shows the DFS according to the pre-treatment cTMN classification, post-treatment pathological nodal status and clinical response to NAC. The pre-treatment clinical stage, clinical response to NAC and post-treatment pathological nodal status were strong predictors of DFS ($P < .0001$, $P = .0005$, $P < .0001$, respectively).

The pathological response results in post-treatment pathological node negative patients are shown in Fig. 3. Pathological node-negative patients accounted for 174 (47%) out of 370 patients. Since the number of Grade 0 patients according to the JBCS system was only two, they were excluded from the analysis. There were no significant relationships between the three pathological response classification systems and the DFS in pathologically node-negative patients. Neither clinical response ($P = .142$) nor pre-treatment clinical stage ($P = .231$) predicted DFS in node-negative patients.

Discussion

Pathological and biological markers predicting "pCR" in NAC have been evaluated in several studies [6, 7], but there is no consensus on the definition of pathological response. It is particularly unclear whether the classification needs the measurement of the extent of therapeutic effect including the disappearance of tumor cells and decrease of tumor cellularity [1–3, 8, 9]. The frequency distribution of residual tumor size was altered markedly by the inclusion of tumor cellularity, and the accurate pathologic response information may be provided the product of pathologic size and tumor cellularity [10]. The results in our study showed that the evaluation of tumor cellularity and tumor size by both Chevallier's and he JBCS classification systems was not useful for predicting prognosis in both all patients and node-negative patients. This result was in contrast to another study, where the reduction of tumor cellularity significantly correlated with the overall and disease free survival [11]. The negative finding in our study may be due to the small sample size of the study and limited number of events in each category of the

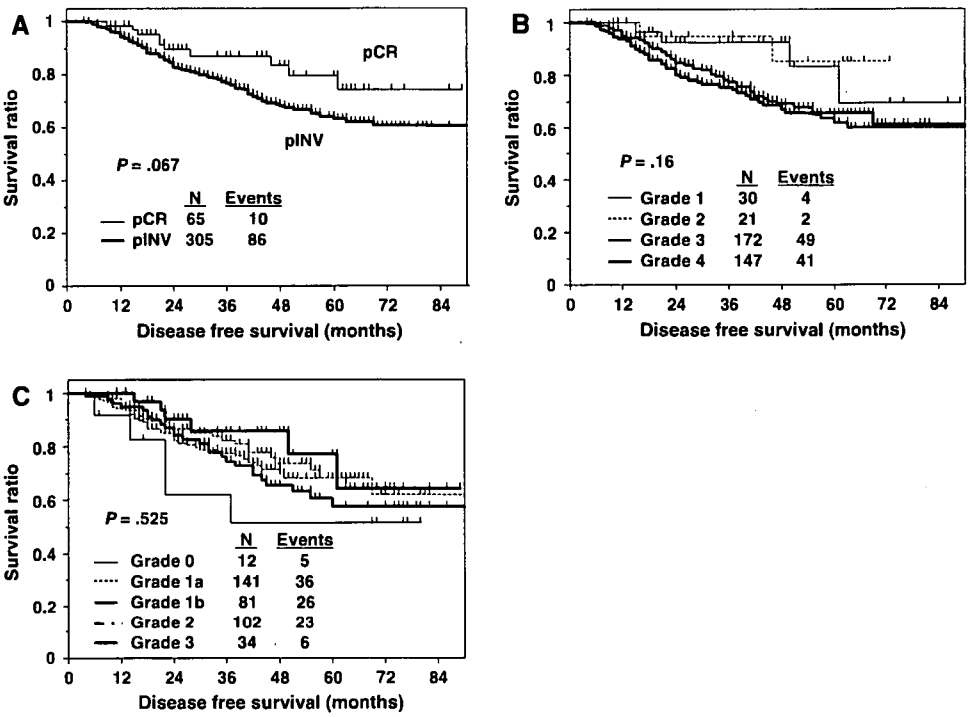

Fig. 1 Kaplan–Meier curves of disease free survival according to pathological response classification systems examined. (**a**) Fisher's classification; (**b**) Chevallier's classification; (**c**) JBCS classification

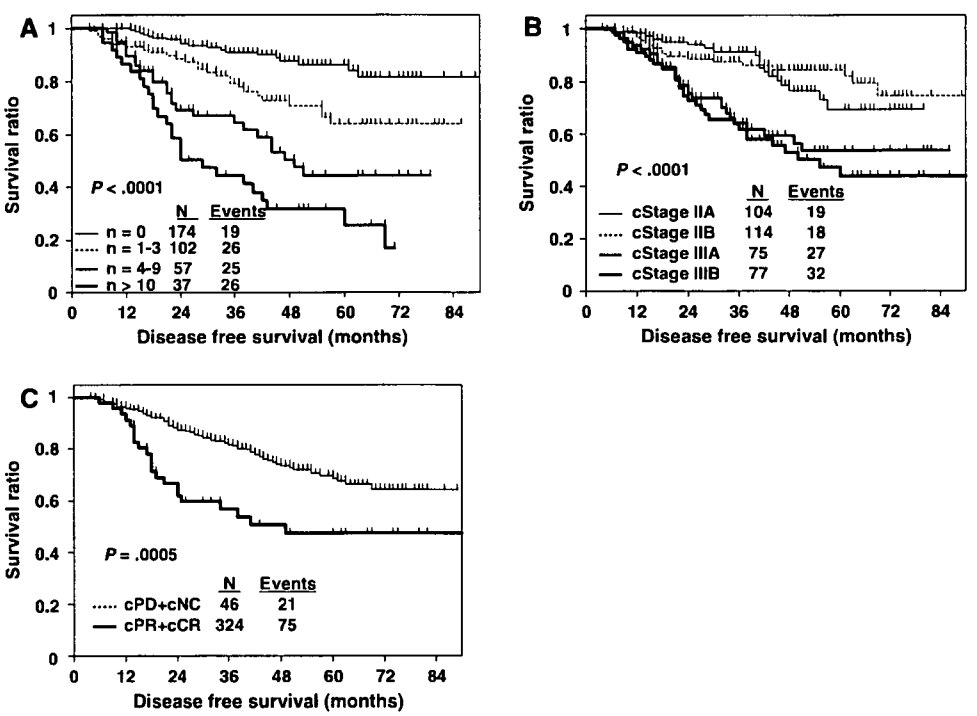

Fig. 2 Kaplan–Meier curves of disease free survival according to (**a**) Pathologic nodal status; (**b**) Clinical staging and (**c**) Clinical response

classification. Moreover the variety of chemotherapy regimens used as NAC may have affected the result. Particularly, trastuzumab was used only in the recent HER2-positive patient cohort.

However, studies including ours indicate the importance of incorporating the pathological nodal status in the prediction of prognosis for patients after NAC [12–15]. Fisher's classification is the most popular classification system using major clinical trials such as NSABP trials, but this classification system is diagnosed simply based on the disappearance of invasive tumor cells, regardless of non-invasive tumor cells, only in the primary tumor. Although Fisher's system is simple, objective and its usefulness as a predictive marker has been validated [1–3, 9, 14], incorporation of the therapeutic effect in axillary lymph nodes may be necessary for more precise outcome prediction.

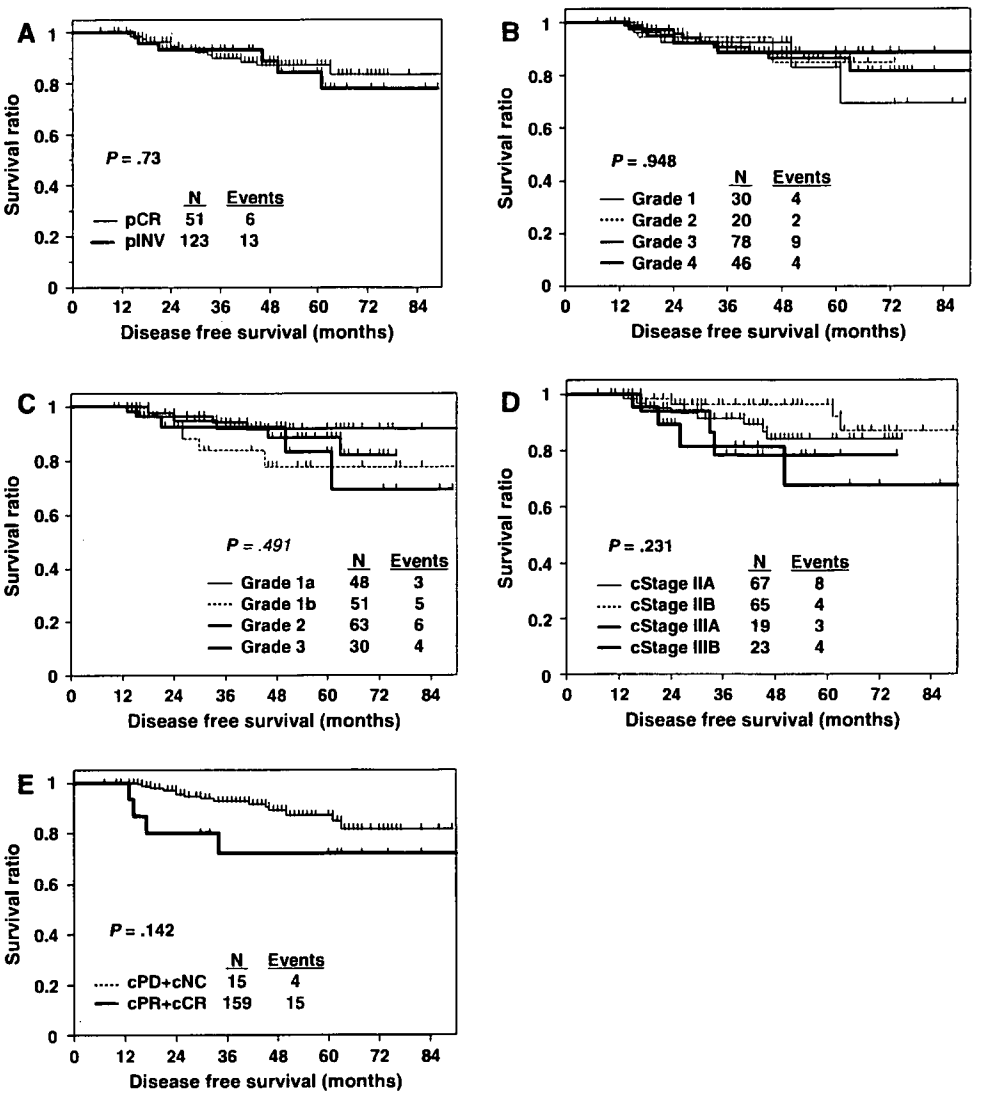

Fig. 3 Kaplan–Meier curves of disease free survival in node negative patients (**a**) Fisher's classification; (**b**) Chevallier classification; (**c**) JBCS classification; (**d**) Clinical staging; (**e**) Clinical response

On the other hand, clinical response was the significant predictor of the disease free survival in this study as reported in several other papers [13, 16–19]. Clinical response reflects the activity of chemotherapeutic agents. Clinical responders had a better prognosis compared with non-responders. The pretreatment clinical stage correlated with disease free survival, but there were good responders among the patients with advanced primary lesions and clinically positive axillary lymph nodes. Although pCR significantly correlated with the clinical response, the importance of the clinical response in outcome prediction may remain in patients with residual tumor or pathologically negative axillary lymph node after NAC.

In conclusion, we think that all three classifications analyzed in this study were not adequate as a prognostic marker of long-term outcome after NAC. The evaluation of the therapeutic effect in primary tumors warrants further study, especially in pathologically node-negative patients after NAC. Given the suggestion that the benefit of certain chemotherapy regimens might be different depending on the biological tumor characteristics (e.g. hormone responsive, HER2, triple negative), the validity of pCR as a prognostic marker might better be tested independently in each biological subset. Moreover, the validity of pCR with NAC including biologically targeted drugs such as trastuzumab should also be revisited.

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CLINICAL TRIAL

Assessment of different criteria for the pathological complete response (pCR) to primary chemotherapy in breast cancer: standardization is needed

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Abstract *Purpose* Evaluation of the safety and efficacy of a combination of docetaxel and doxorubicin in breast cancer patients. Evaluation and comparison of the pathological complete response (pCR) to this regimen according to various definitions in different clinical trials. Utilize the data to propose standardization of definitions. *Patients and Methods* Between 1998 and 2001, 141 patients with stage II (tumor size >3.0 cm) or III breast cancer were treated with doxorubicin 50 mg/m^2 followed by docetaxel 60 mg/m^2 (AT) on day 1. A total of 4 courses of AT were administered as primary chemotherapy with intervals of 3 weeks. Additionally, 2 cycles of the same regimen were administered after surgery when clinical CR or PR was achieved; otherwise, 4 cycles of CMF were added postoperatively. *Results* 141 patients were enrolled in this trial. A clinical response rate was 86%. Seven patients (5%) achieved pCR according to the Japanese Breast Cancer Society classification, 14 patients (10%) fulfilled the University of Texas M.D. Anderson Cancer Center trial's pCR criteria, and 19 patients (14%) met the NSABP trial pCR definition. NCI CTC version 2 grade 3/4 toxicities included leucopenia (26%), neutropenia (85%) and febrile neutropenia (12%). *Conclusion* Primary chemotherapy with AT induced modest tumor responses with tolerable toxicity. Differences in the definition of pCR among clinical trials caused substantial confusion in interpreting the trial results. Therefore, standardization of the pCR definition after primary chemotherapy is needed.

Keywords Aberdeen classification · Docetaxel · Doxorubicin · GEPARDO Trial · Japanese Breast Cancer Society · NSABP · Pathological complete response · Primary chemotherapy · University of Texas M.D. Anderson Cancer Center

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Introduction

It is now widely accepted that primary chemotherapy achieves high clinical response rates and allows conservative surgery in more patients with breast cancer without compromising the prolonged disease-free and overall survival rates that were achieved after postoperative chemotherapy [1–5]. Tumor shrinkage by the primary chemotherapy can be easily monitored clinically both by physicians and patients [6]. For physicians, continuation of treatment is reasonably determined based on efficacy. For patients, compliance with the scheduled courses of chemotherapy is increased because they, themselves, experience the efficacy, which helps them mentally to overcome the unpleasant adverse effects. The pathological response to the primary chemotherapy provides reliable prognostic information [7]. Patients with a pathological complete response (pCR) have significantly longer disease-free and overall survival as compared to patients in lower pathological response categories [1]. However, the definitions used for the evaluation of pCR vary among clinical

trials. For example, the Japan Breast Cancer Society defines pCR as no remaining cancer cells, or necrotic or non-viable residual cancer cells [8], and the German Prospective Adriamycin–Docetaxel (GEPARDO) Trial defines pCR as no microscopic evidence of viable tumor cells in resected specimens [9, 10]. In contrast, the definition adopted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B 18 trial allows specimens with intraductal residual tumor cells [1]. The trial of the University of Texas M.D. Anderson Cancer Center (M.D. Anderson) pCR criteria requires not only complete response of the primary lesion but also the disappearance of axillary lymph node metastasis [11]. The differences in the definition of pCR among clinical trials cause substantial confusion in interpreting the trial results. Standardization of the definition of pCR after primary chemotherapy is, therefore, essential. We tested the clinical and pathological responses to the combination of two of the most active cytotoxic agents, Doxorubicin (A) and Docetaxel (T), in patients with stages II or III breast cancer and compared pathological responses using several definitions. These agent have shown no cross-resistance and have different toxicity profiles [12–14].

Patients and methods

Patient population

A patient had to meet the following inclusion criteria to be enrolled into the trial, which had been approved by the Institutional Ethics Review Committee: Breast cancer confirmed histologically with core needle biopsy or incisional biopsy specimen; stage II (tumor size $\geq$3.0 cm in largest diameter by palpation) or III using the 1997 International Union Against Cancer (UICC) classification system; less than 70-years-old; tumor estrogen receptor-negative or progesterone receptor-negative; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1; adequate hematological, renal, and hepatic functions (WBC count $\geq$4,000/mm^3 or the absolute neutrophil count $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, serum creatinine $\leq$1.5 mg/100 ml, AST $\leq$80 IU/l and total bilirubin $\leq$1.5 mg/100 ml); normal electrocardiography; and written informed consent.

Patients were excluded from participation for the following reasons: Previous treatment for breast cancer; previous cancer with a disease-free interval of less than 5 years or a second primary malignancy; active infection; psychiatric illness; cardiac disease or other significant illness that might influence the tolerability of the treatment; and pregnancy or breast-feeding.

Study treatment

The regimens used were doxorubicin 50 mg/m^2 as a 1-h intravenous infusion, followed by docetaxel 60 mg/m^2 as a 1-h infusion on day 1. A total of four courses were administered with intervals of 3 weeks between courses. All patients received premedication consisting of dexamethasone (8 mg) and granisetron hydrochloride (3 mg) before doxorubicin administration. Oral dexamethasone, 4 mg, was continued twice daily on day 2 and once daily on days 1 and 3 after chemotherapy. Antibiotic prophylaxis could be given to patients with febrile neutropenia during the first course. Additional antiemetic treatment could be prescribed if needed.

Patients who achieved clinical CR or PR to this regimen received 2 additional cycles of the same regimen after surgery. Patients with SD or PD received a mastectomy when the tumor was operable, followed by 4 cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5FU 600 mg/m^2, all intravenously, once every 3 weeks).

All patients who were tumor estrogen receptor-positive or progesterone receptor-positive received tamoxifen 20 mg a day for 5 years after chemotherapy.

Median follow-up time was 36 months (range, 5 to 60 months).

Dose modification

Therapy could be postponed for a maximum of 3 weeks if the WBC count was $<$3,000/mm^3 or the absolute neutrophil count was $<$1,500/mm^3, platelet count was $<$100,000/mm^3, serum creatinine was $>$1.5 mg/100 ml and total bilirubin was $>$1.5 mg/100 ml. If patients did not recover from toxicity during this period, protocol treatment had to be discontinued, and surgery was recommended. During the treatment, if febrile neutropenia lasted for $\geq$5 days, the platelet count was $\leq$25,000/mm^3, or any grade 3 or 4 (National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2) nonhematological toxicity occurred—except for alopecia, nausea, and vomiting—the dose of docetaxel was reduced to 50 mg/m^2 in the next cycle. These dose reduction adjustments were maintained during subsequent cycles.

Surgery and radiation therapy

After completion of chemotherapy and clinical assessment of response, patients underwent appropriate surgery according to the size and location of the primary tumor. If the tumor was still too large for breast-conserving surgery,

mastectomy was recommended. If the tumor size allowed breast-conserving surgery, then the surgical margins had to be free of invasive or noninvasive breast cancer at a width of at least 1 mm; otherwise, repeat excision had to be performed.

All patients who underwent breast-conserving surgery or who were diagnosed as stage III at study entry received radiotherapy. Radiotherapy was delivered with a dose of 50 Gy in 25 fractions over 5 weeks using tangential fields to the chest wall or regional lymph nodes.

Trial assessments

The diagnosis was established with core needle biopsy or incisional biopsy specimens of the primary tumor. Nuclear grade was assessed by histopathological evaluation; estrogen and progesterone receptors and HER2 status were determined by immunohistochemistry. The pretreatment work-up included a complete history and physical examination, complete blood cell counts with differential and platelet counts, blood chemistry analysis, electrocardiography, chest radiography, breast computed tomography, abdominal ultrasonography, bone scan, bilateral mammography and breast ultrasonography. The size of the breast tumor and axillary nodal status was determined by palpation. In patients with multifocal or multicentric breast tumors, the lesion with the largest diameters was targeted for follow-up.

The clinical response to primary chemotherapy was classified with palpation by the following criteria: complete response (CR), a total resolution of the breast tumor based on physical examination; partial response (PR), a 50% or greater reduction of the product of the two largest perpendicular dimensions of the breast mass; progressive disease (PD), a 25% or greater increase in the size of the breast mass or the appearance of a new lesion; Stable disease (SD), not showing enough change in disease status to be defined as PR or PD.

The pathological response to primary chemotherapy was evaluated using definitions employed by five clinical trials. The Japanese pathological response criteria was characterized as grade 3 (pCR) when there was no cancer cells, or necrotic or non-viable residual cancer cells; grade 2, severe cellular injury or replacement of 2/3 or more of the cancer cells; grade 1b, severe cellular injury or replacement of 1/3 to 2/3 of the cancer cells; grade 1a, mild cellular injury in a portion of the cancer cells, or severe cellular injury or replacement of less than 1/3 of the cancer cells by fibroblasts, histiocytes or fibrosis; grade 0, no histological change in the cancer cells [8]. The Aberdeen classification characterized grade 1 as, some alteration to individual malignant cells but no reduction in overall number; grade 2, a minor loss of invasive tumor cells but overall cellularity still high; grade 3, a moderate reduction in tumor cells with up to an estimated 90% loss; grade 4, a marked disappearance of invasive cells such that only small clusters of widely dispersed cells are detected; grade 5, no invasive cells identifiable in sections from the site of the previous tumor, i.e., only in-situ disease or tumor stroma remained [15]. The GEPARDO classification characterized grades 0 and 1 as, "no effect" and "resorption and tumor sclerosis," respectively; grade 2, minimal focal invasive tumor residues of less than 5 mm in diameter are found; grade 3, only in situ tumor residues are found; grade 4, not a single viable tumor cell could be detected [9]. In the NSABP B18 classification, pINV was defined as histological evidence of invasive cells among complete clinical responders; pCR, no histological evidence of invasive cells among complete clinical responders [1].

Although four definitions evaluate the primary lesion only, the M.D. Anderson trial's pCR criteria also require the evaluation of axillary lymph nodes [11].

All patients who received at least one course of chemotherapy were assessable for toxicity. NCI CTC version 2 was used for evaluation.

Statistical considerations

The primary study end point was the clinical response rate. We estimated that a total sample size of 140 patients would be required to allow for 130 assessable patients. This sample size was required to demonstrate an anticipated clinical response rate of 80% with confidence intervals of 72–86% at an alpha of 0.05.

Recurrence-free survival was defined as time on study before local, regional, or distant tumor recurrence; second primary cancers, contralateral events, and deaths without evidence of disease were treated as censoring events. Patients who died without documented tumor recurrence were censored on the day of death or last follow-up. Patients who did not expire were censored at the time they were last known to be alive. The Kaplan–Meier curve [16] was used to estimate the recurrence-free survival of patients who entered this study.

Results

Between May 1998 and August 2001, 141 patients (median age, 49 years; range, 29–69 years) were enrolled in this study. The characteristics of the patients are summarized in Table 1. The median diameter of the largest primary tumor was 5.3 cm (3.0–12 cm), with 45% T2 tumors, 31% T3 tumors and 24% T4 tumors. A total of 92 patients had

Table 1 Patient characteristics

	No. of patients	%
Age, years		
Median (range)	49 (29–69)	
Tumor size by palpation, cm		
Median (range)	5.3(3–12)	
T2	64	45
T3	44	31
T4	33	24
Axillary nodal status		
Negative	78	55
Positive	63	45
Stage		
IIA	42	30
IIB	45	32
IIIA	20	14
IIIB	34	24
ER and PR		
Both negative	49	35
Either one positive	92	65
HER2		
3+	11	8
Others	130	92
Histological type		
Invasive ductal	117	82
Invasive lobular	8	6
Others	16	12
Histological grade		
1	3	2
2	61	43
3	62	44
Not assessed	15	11

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; DCIS, ductal carcinoma in situ

hormone receptor-positive tumors and 11 patients had HER2 overexpression. A total of 83% of tumors were invasive ductal carcinoma, whereas 5.6% were intraductal carcinoma.

Dose administration

Patients received a total of 560 cycles of doxorubicin and docetaxel. Chemotherapy was administered without dose reduction in 45 patients. The dose intensity of A and D were 94% and 76%, respectively.

Clinical response

A tumor response was assessed in 141 patients. The clinical response rate was 86% (95% Confidence Interval (CI): 78.9–91.1). Clinical CR was attained in 24 patients (17%), PR in 97 patients (69%), SD in 17 patients (12%) and PD in three patients (2%). Table 2 shows the number of responding patients during the chemotherapy. One PD patient underwent surgery after chemotherapy, two PD patients were not operable due to the extent of tumor progression. One patient who achieved PR refused surgical treatment.

Pathological response

The results of the pathological examination after chemotherapy were available for 138 patients. In seven patients (5%: 95%CI, 2.1–10.2), no tumor cells could be detected (the Japanese criteria, grade 3; the GEPARDO criteria, grade 4). In a further 12 patients (14%: 95%CI, 8.5–20.7), only intraductal cancer cells were found (defined as pCR in the NSABP 18 criteria and as pCR, grade 5 by the Aberdeen criteria), and in 25 patients, minimal focal invasive tumor residues of less than 5 mm in diameter were reported (defined as grade 2 in the GEPARDO criteria). A total of 14 patients (10%: 95%CI, 5.7–16.4) fulfilled the M.D. Anderson pCR criteria (Table 3). Thus, significant signs of pathological regression (grade 3 and grade 2 according to the Japanese criteria) of the primary tumor were reported in 49 patients (36%).

Rate of breast-conserving surgery

It was possible to conserve the affected breast in 31% of the patients. The rates of breast conservation were 40%, 27% and 12% in tumors with initial palpable sizes of $\geq$3 cm but less than 5 cm ($n = 65$), $\geq$5 cm but less than 7 cm ($n = 55$), and $\geq$7 cm ($n = 17$), respectively. The odds of conserving the breast were highly dependent on the initial palpable size of the tumor and the clinical response to primary chemotherapy.

Table 2 Clinical tumor response during primary chemotherapy number of responding patients after each cycle of chemotherapy

Cycle	1	2	3	4
CR ($n = 24$)	2	15	24	24
PR ($n = 97$)	40	71	86	97
NC ($n = 17$)	99	54	29	17
PD ($n = 3$)	0	1	1	1

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Table 3 Pathological complete response rates by each trial definition criteria

	Japan GEPARDO		NSABP Aberdeen		M.D. Anderson	
	No. of patients	%	No. of patients	%	No. of patients	%
pCR	7	5	19	14	14	10
Non pCR	131	95	119	86	124	90

Abbreviations: NSABP, the National Surgical Adjuvant Breast and Bowel Project; GEPARDO, the German Prospective Adriamycin–Docetaxel Trial; M.D. Anderson, The University of Texas M.D. Anderson Cancer Center.

Recurrence-free survival

Figure 1 shows the recurrence-free survival. The median follow-up time was 36 months (range, 5–60 months). The 3-year recurrence-free survival is 74.6%.

Toxicity

All 141 patients who received at least one course of chemotherapy were assessable for toxicity. Table 4 shows the figures for NCI CTC version 2 grades 3/4 hematological and nonhematological toxicities. Leukopenia reached grade 3/4 in 26% of the patients, and grade 3/4 neutropenia was recorded in 85% of them. The incidence of febrile neutropenia was 12%. Only three patients were hospitalized due to this event. Other frequent toxicities, apart from alopecia, were nausea, vomiting, stomatitis and diarrhea.

Discussion

Breast cancer is widely regarded as a systemic disease [17, 18]. Preoperative administration of systemic therapy

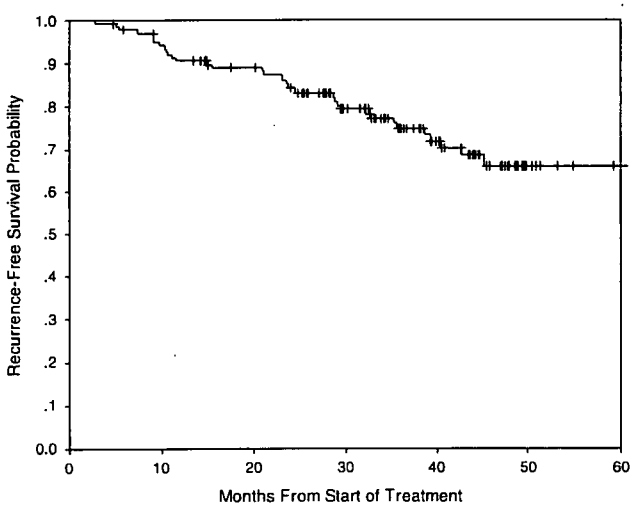

Fig. 1 Kaplan–Meier analysis of recurrence-free survival time

Table 4 Hematological and nonhematological Toxicities (NCI-CTC Version 2.0)

	Grade 1/2 (%)	Grade 3/4 (%)
Anemia	50	0
Leukopenia	30	26
Neutropenia	14	85
Thrombocytopenia	5	0
Nausea	74	2
Vomiting	25	1
Diarrhea	15	2
Febrile neutropenia	–	12
Infection	11	0
Stomatitis	51	0
Neuropathy	6	0
Peripheral edema	2	0
Nail change	7	0
Phlebitis	4	1

Abbreviation: NCI-CTC, the National Cancer Institute Common Toxicity Criteria

therefore represents a logical step in improving the efficacy of treatment. Many studies have reported that primary chemotherapy induced survival improvement that was comparable to that achieved with postoperative chemotherapy [19–21]. In addition, this therapy significantly improves the rate of breast-conserving surgery, and pCR serves as an important prognostic indicator [1, 7].

Newer regimens, including more active agents in primary chemotherapy, must have a potential to improve efficacy. In order to compare different primary chemotherapeutic regimens, it is important to use pCR as a primary endpoint in evaluating each regimen [22].

In defining pCR, some investigators evaluate it based on the state of the primary lesion alone, whereas others evaluate it based on the states of both the primary lesion and axillary lymph nodes; a consensus has not been reached among the clinical trial groups. For example, the NSABP B 18 trial regarded patients as pCR if their primary lesion had disappeared. Therefore, in some patients who were evaluated as having achieved pCR according to this criterion, metastatic foci remained in the axillary lymph nodes. Aberdeen's pCR criteria, which is used at the University of Aberdeen (United Kingdom), is also based on this definition. In the M.D. Anderson Cancer Center trial, patients were evaluated as pCR if both the primary lesion and axillary metastasis had disappeared.

With respect to evaluation of the primary lesion, some investigators define pCR as the complete disappearance of cancer cells, whereas others allow the presence of intraductal residual tumor cells. Several kinds of criteria established in Japan and in Germany, GEPORDO, are

based on the former definition of pCR, whereas other kinds of criteria established by the trials of NSABP B18, Aberdeen, and M.D. Anderson Cancer Center are based on the latter definition.

In addition, the criteria for preparing pathological specimens have not been standardized. Further investigations with thinner resected specimens may decrease the rate of pCR. In this study, we cut the primary lesion and its periphery to a thickness of 1.5 cm from surgical specimens in patients who underwent mastectomy, and cut surgical specimens to a thickness of 1 cm to prepare pathological specimens from patients who underwent breast-conserving surgery.

Among these criteria, those that appear to provide reasonably accurate predictions of the prognosis during long-term follow-up will be mainly employed among clinical trials in the future. At the present time it is not possible to tell which of these criteria should be preferably used because the follow-up periods have been too short. For an analysis of the criteria to use for obtaining the most accurate prognosis, a sufficient number of patients and thorough follow-up are needed; currently, only the NSABP B18 trial meets these conditions [23]. However, the NSABP criteria differ from the criteria used in Japan and Europe.

Thus, to summarize, the criteria for the pathological response to primary chemotherapy have not been standardized. Therefore, values should not be simply compared when the efficacy of chemotherapeutic regimens are evaluated based on the pCR rates.

In the future, primary chemotherapy will be performed in an increasing number of patients; therefore, standardized pathological criteria should be established.

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Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

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Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

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Key words: stage IVb cervical carcinoma, prognostic factor, chemotherapy, performance status

Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ

metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph node metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

Table I. Patient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

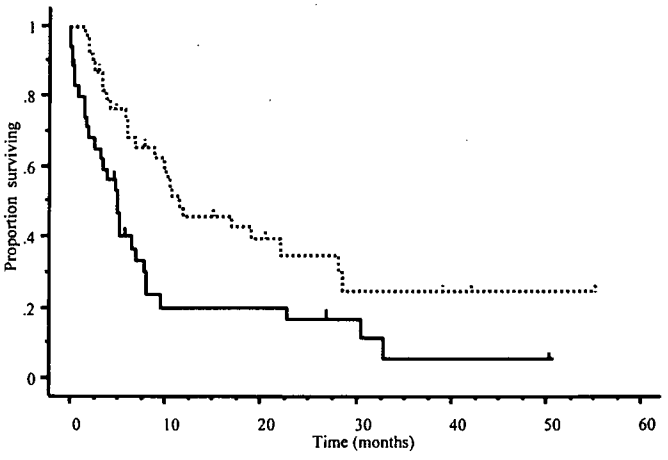

Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9%
					(95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

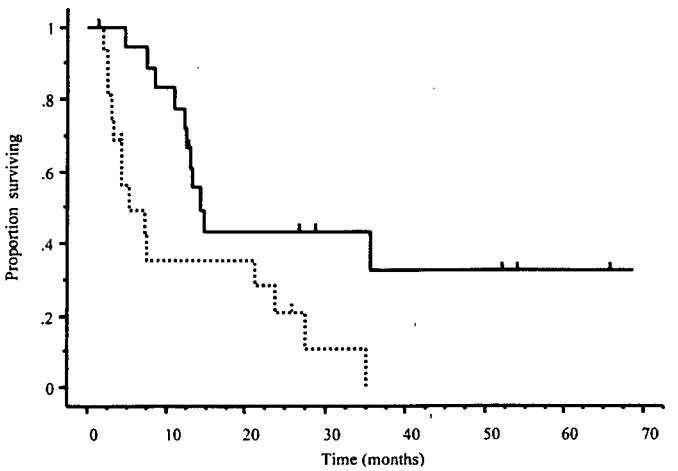

Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

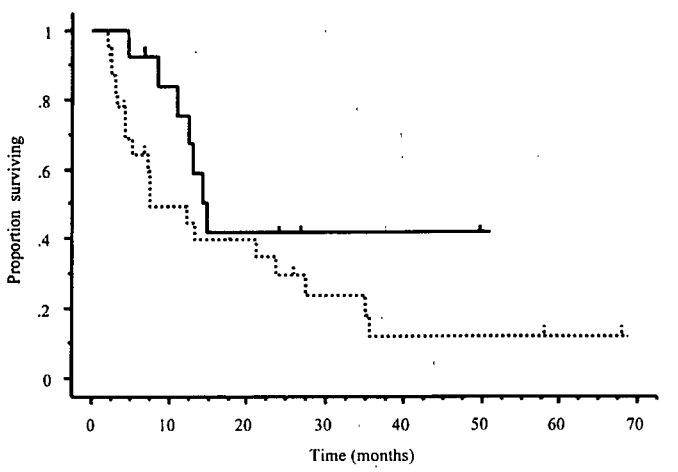

Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived

Table V. Prognostic factors of overall survival.

Factor	Univariate P-value	Multivariate P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

used as a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

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