cells, we treated her with anthracyclines in consolidation therapy. Beaumont et al. indicated that the survival of tAPL was 59% at 8 years and that the preponderance for primary malignancy of patients with tAPL was breast cancer. The interval between the primary malignancy and secondary leukemia was less than 5 years in most cases (1,5,19). Because metastatic breast cancer patients may achieve long-term survival, the possibility of secondary malignancies should be careful monitored.

In case of this patient, because her complete blood count did not fully recover and a bone marrow biopsy disclosed that bone metastases of breast cancer cells had progressed after the first consolidation chemotherapy for tAPL, the subsequent consolidation chemotherapy for tAPL was interrupted and chemotherapy for breast cancer was forced to start, resulting in a possibly insufficient treatment for tAPL. Considering the palliative nature of the treatment of metastatic breast cancer patients, the priorities and goals of treatment should be carefully considered—with thought given to whether the breast cancer or the secondary malignancy is the life-limiting disease. Even if intensive treatment for tAPL is considered, if the tAPL becomes refractory to induction and consolidation chemotherapy, high-dose chemotherapy supported by hematopoietic stem cell transplantation might not be indicated because of the incurable breast cancer bone metastases.

In conclusion, we have reported a case of tAPL in a patient with breast cancer who had not undergone chemotherapy. Although the present case is thought to be rare, patients should be carefully monitored for secondary malignancies like tAPL. Simultaneously, the possibility that multimodality treatments, including the use of various cytotoxic agents, such as alkylating agents and topoisomerase II inhibitors, may cause secondary malignancies as well as contributing to the long-term survival of patients with breast cancer must be kept in mind. For patients with secondary malignancy and advanced primary disease, the treatment priorities must be carefully considered.

Acknowledgments

We thank Yukio Kobayashi (Hematology Division, National Cancer Center Hospital) and Akiko Maeshima (Pathology Division, National Cancer Center Hospital) for histopathological diagnosis and preparing the figure.

Conflict of interest statement

None declared.

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J Cancer Res Clin Oncol
DOI 10.1007/s00432-008-0488-x

ORIGINAL PAPER

Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy

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Received: 31 May 2008 / Accepted: 17 September 2008

Abstract

Background Limited information is available regarding the usefulness of third-line chemotherapy for recurrent ovarian, fallopian tube, and primary peritoneal cancer treated with platinum-taxane regimens as first-line therapy.

Patients and methods We retrospectively reviewed the medical records of women with ovarian, fallopian tube, and primary peritoneal cancer who were treated at the National Cancer Center Hospital between 1999 and 2005 to investigate the relations of clinicopathological factors to important clinical endpoints such as the response rate (RR), time to progression (TTP) and overall survival (OS) after third-line chemotherapy.

Results A total of 172 patients received first-line platinum/taxane regimens during the study period, among whom 111 had disease progression after first-line chemotherapy. Eighty-one of these 111 patients received second-line chemotherapy, and 73 had disease progression. Fifty-four of the 73 patients with disease progression received third-line chemotherapy. The RR to third-line chemotherapy was 40.7% (95% CI, 27.6–53.8%). The median TTP was 4.4 months (range 0–19.5 months), and the median OS was 10.4 months (range 1.5–44.3 months). Performance status (PS) and primary drug-free interval (DFI) were independent predictive factors for the RR to third-line chemotherapy ($P = 0.04$ and $P = 0.009$). PS and primary DFI were also independent predictive factors for TTP and OS on multivariate analysis ($P = 0.006$, $P = 0.005$ and $P = 0.01$, $P = 0.004$, respectively).

Conclusions PS and primary DFI are useful predictors of the response to third-line chemotherapy in women with recurrent ovarian, fallopian tube, and primary peritoneal cancer. In this setting, however, both of these variables are subject to several well-established potential biases and limitations; further prospective studies are thus needed.

Keywords Third-line chemotherapy · Recurrent ovarian · Fallopian tube · Primary peritoneal cancer

Introduction

Ovarian cancer remains the leading cause of death from gynecological neoplasms in the Western world (Greenlee et al. 2001). Most cases are diagnosed when the disease is advanced, resulting in poor survival (Heintz et al. 2001; Engel et al. 2002; Jemal et al. 2003). Despite high rates of objective responses to surgery and primary chemotherapy, relapse rates remain high. Recurrent disease is treated either with the same regimen as that used for first-line chemotherapy (i.e., reinduction therapy) or with second- or third-line regimens. The aim of treatment after relapse is mainly palliative, designed to control disease symptoms, maintain patients' quality of life, and prolong survival. New chemotherapeutic drugs have yielded objective response rates

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(RR) of 10–30% in recurrent ovarian cancer, depending on the anticancer activity of the drug(s) used, cross-resistance with previously administered drugs, and the response of the primary tumor to platinum compounds. In general, primary platinum sensitivity is defined as a documented response to the initial platinum-based therapy for at least 6 months after the end of treatment. RR of 30% to >50% have been obtained in patients with longer treatment-free intervals or with platinum-sensitive primary tumors (primary platinum sensitivity) as compared with only <20% in patients with shorter treatment-free intervals (platinum resistance of the primary tumor) or refractory ovarian cancer (no remission in response to first-line therapy) (Blackledge et al. 1989; Markman et al. 1991; Thigpen et al. 1994). Most previous studies have focused on the overall tumor response and time to treatment failure for specific drugs rather than attempting to evaluate the overall response to second-, third-, or fourth-line chemotherapy. The aim of this retrospective study was to investigate the relations of clinicopathological factors to important clinical endpoints such as the RR, time to progression (TTP), and overall survival (OS) in response to third-line chemotherapy in women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who received platinum/taxane regimens as first-line therapy.

Patients and methods

Patients

We retrospectively reviewed the medical records of patients with ovarian, fallopian tube, and primary peritoneal cancer treated at the National Cancer Center Hospital between 1999 and 2005. All the patients had received platinum/taxane regimens as first-line therapy. Treatment decisions were usually made by the attending clinician. Patients in whom the tumor was considered possibly platinum-sensitive usually received a platinum agent, a taxane, or both. In general, combination chemotherapy was not administered as salvage treatment for recurrent disease, and most patients with recurrent disease received a single chemotherapeutic agent. Drug-free interval (DFI) was measured from the date of the last dose of chemotherapy until disease progression. Primary DFI was measured from the date of last dose of first-line chemotherapy until disease progression, and secondary DFI was measured from the date of the last dose of second-line chemotherapy until disease progression. Patients participated in clinical trials if they were eligible. The imaging criteria for treatment response were based on two-dimensional measurements of the lesions. Serum CA125 levels were not used as a primary measure of the response, but were referred to in the evaluation of response. Complete response was defined as no evidence of disease on physical examination or imaging studies, with normalization of the serum CA125 level. Partial response was defined as a >50% reduction in tumor size. Stable disease was defined as a 25–50% decrease or increase, or as no change in tumor size. Patients with an increase in the serum CA125 level were not evaluated to have had a partial response or stable disease. Progressive disease was defined as a >25% increase in tumor size. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were not used because most patients received treatment before this system was adopted by our hospital.

Statistical analysis

The main outcome measures for drug efficacy were RR, TTP, and OS. TTP was defined as the interval from the first day of third-line chemotherapy to the day of documented disease progression. For patients who were alive at the end of the study, the TTP data were right-censored to the time of the last evaluation or the time of the last contact at which the patient was progression-free. OS was defined as the interval from the first day of third-line chemotherapy to the day of death. For patients who were alive at the end of the study, the OS data were right-censored to the time of the last evaluation or contact. Data were analyzed by parametric and nonparametric statistics using SAS, version 9.1.3 (SAS Institute, Cary, NC, USA). Descriptive statistics were used for demographic data; such data are presented as mean with standard deviations or as medians with ranges. Survival was estimated using the Kaplan–Meier method, and differences between survival curves were evaluated with the log-rank test. A multivariate logistic regression analysis was performed to determine predictive factors of the response to chemotherapy. A Cox regression analysis was performed to determine factors influencing TTP and OS.

Results

A total of 172 patients received first-line platinum/taxane regimens during the study period, of whom 111 had disease progression after first-line chemotherapy. Eighty-one of these 111 patients received second-line chemotherapy, among whom 73 had disease progression. Fifty-four of these 73 patients received third-line chemotherapy (Fig. 1). Mean age at the time of diagnosis of the primary cancer was 54 years (26–75 years), and mean age at the start of second- and third-line chemotherapy was 55 (28–76 years) and 55 (31–77 years) years, respectively. There were 46 cases (85.1%) of ovarian carcinoma, 7 (13.1%) of primary peritoneal carcinoma, and 1 (1.8%) of fallopian tube carcinoma. The patients' characteristics are shown in Table 1.

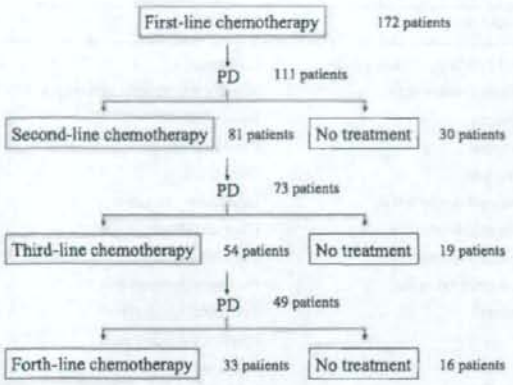

Fig. 1 Schema of treatment

At the time of initial recurrence, 37 patients (69%) had primary platinum sensitivity, and 17 (31%) had primary platinum resistance. All patients treated with second-line drugs had either stable or progressive disease and received third-line treatment within 1–2 months after the last cycle of second-line treatment. The most commonly used regimen was weekly paclitaxel/carboplatin for second-line treatment and carboplatin for third-line treatment. The numbers of patients and chemotherapeutic drugs used in each setting are listed in Table 2. The median number of cycles of third-line treatment was 6 (range 1–18 cycles). The median TTP was 4.4 months (range 0–19.5 months), and the median OS was 10.4 months (range 1.5–44.3 months) (Fig. 2). The RR to third-line chemotherapy was 40.7% (95% CI; 27.6–53.8%). Five patients (9.2%) had complete responses and 17 (31.5%) had partial responses. Disease remained stable in 18 patients (33.3%) and progressed in 12 (22.2%). Two patients discontinued treatment because of hypersensitivity reactions to carboplatin. Overall, 49 patients had disease progression and 33 subsequently received fourth-line chemotherapy. The RR to fourth-line chemotherapy was 36.3% (95% CI, 19.9–52.7%); 2 patients had complete responses, 7 had partial responses, 9 had stable disease, and 12 had progressive disease. At the time of data analysis, 38 of the 54 patients (70.3%) had died. We studied the relations between the response to third-line drug therapy and clinical factors such as age, performance status (PS), histopathological type of cancer, number of target lesions, primary and secondary DFI, response to second-line chemotherapy, and the use of platinum/taxane regimens. The RR to third-line treatment was found to be significantly better in patients with a good PS (0 or 1) and a primary DFI of >6 months ($P = 0.04$ and $P = 0.009$, respectively, Table 3). Patients with a good PS and a primary DFI of >6 months also had a longer TTP and better OS ($P = 0.006$, $P = 0.005$ and $P = 0.01$, $P = 0.004$, respectively, Table 4). Median OS was slightly but not significantly better in the patients who responded to third-line chemotherapy (15.1 months; range 2.4–33.7 months) than in those who did not (9.4 months; range 1.5–44.3 months) ($P = 0.054$, Fig. 3). Median OS was significantly longer in the patients who received fourth-line chemotherapy (8.2 months; range 2.1–25.2 months) than in those who did not receive chemotherapy (2.4 months; range 0.2–16.2 months) ($P < 0.0001$, Fig. 4).

Table 1 Patient characteristics ($n = 54$)

Age (year)	Median (range)
At primary diagnosis	54 (26–76)
At second-line chemotherapy	55 (28–77)
At third-line chemotherapy	55 (31–78)
Performance status	
0	6
1	22
2	24
3	2
Stage	
I	4
II	5
III	30
IV	15
Organ	
Ovarian carcinoma	46
Primary peritoneal carcinoma	7
Fallopian tube carcinoma	1
Pathology	
Serous adenocarcinoma	40
Endometrioid adenocarcinoma	2
Mucinous adenocarcinoma	1
Clear cell carcinoma	5
Undifferentiated carcinoma	6
No. of target lesions	
1	38
2	10
3	6
Drug free-interval (month)	
Primary	8.2 (0.9–39.3)
Secondary	8.3 (0.1–21.5)
3rd-line regimens	
Platinum/taxane-containing regimens	36
Other regimens	18

Discussion

In women with ovarian cancer, treatment goals after failure to respond to first-line therapy are (1) the control or prevention

Table 2 First-, second- and third- line chemotherapeutic regimens used

First-line		Second-line		Third-line	
Paclitaxel/carboplatin	35	Weekly paclitaxel/carboplatin	28	Carboplatin	14
Docetaxel/carboplatin	12	Docetaxel/carboplatin	12	Weekly paclitaxel/carboplatin	10
Paclitaxel/cisplatin	7	Irinotecan	5	Irinotecan	8
		Topotecan	2	Irinotecan/etoposide	4
		Carboplatin	2	Docetaxel	4
		Liposomal doxorubicin	1	Liposomal doxorubicin	4
		Paclitaxel/carboplatin	1	Docetaxel/carboplatin	3
		Irinotecan/carboplatin	1	Cisplatin	2
		Irinotecan/etoposide	1	Paclitaxel/carboplatin	1
		Docetaxel	1	Paclitaxel/cisplatin	1
				Irinotecan/mitomycin	1
				Paclitaxel	1
				Etoposide	1

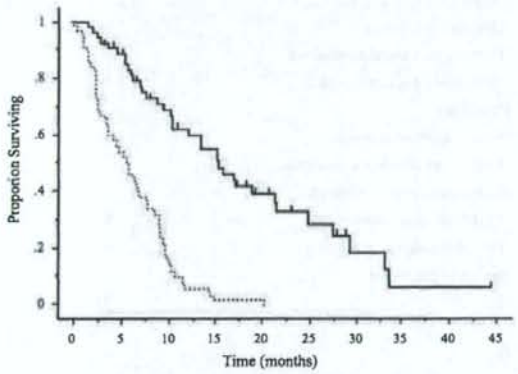

Fig. 2 Kaplan–Meier analysis of time to progression (*solid line*) and overall survival (*dotted line*) following third-line chemotherapy. *Vertical bars* indicate censored cases

of disease-related symptoms, (2) the maintenance of a good quality of life, and (3) the prolongation of progression-free survival. The aims of salvage treatment have long been a matter of debate. The possibility of achieving an OS benefit in these patients is very limited. RRs are generally similar to or poorer than those with previous treatments are. Moreover, the increased risk of toxicity in patients with a history of previous treatment(s) and of negatively affecting performance status makes some physicians reluctant to continue drug treatment.

Patients who have good performance status without clinically significant comorbidity may wish to continue treatment (Doyle et al. 2001). Donovan et al. (2002) evaluated the treatment preferences of women with recurrent ovarian cancer and reported that most patients (86%) initially prefer subsequent therapy, with 25% never considering the withdrawal of chemotherapy, even when the expected median survival was <1 week. Physicians must therefore take into account patients' wishes along with other clinical data when planning treatment.

Table 3 Multivariate analysis of response rates to third-line chemotherapy

Clinical factors	No. of patients	Response rate (95% CI)	*P* value
Age			
<60	35	52.6% (30.1–75.0%)	0.50
≥60	19	44.0% (23.7–56.2%)	
PS			
0,1	28	57.1% (38.8–75.4%)	0.04
2,3	26	30.7% (13.0–48.5%)	
Pathology			
Mucinous/clear cell	6	33.3% (4.3–71.0%)	0.22
Non-mucinous/clear cell	48	45.8% (31.7–59.9%)	
No. of target lesions			
1	40	45.0% (29.5–60.4%)	0.37
2,3	14	42.8% (16.9–68.7%)	
Primary DFI			
<6 months	17	17.6% (0.4–35.7%)	0.009
≥6 months	37	51.3% (35.2–67.4%)	
Secondary DFI			
<6 months	33	42.4% (25.5–59.2%)	0.70
≥6 months	21	47.6% (26.2–68.9%)	
Response to second-line therapy			
Responders	35	45.7% (29.2–62.2%)	0.09
Non-responders	19	31.5% (10.6–52.4%)	
PT regimens			
PT regimens	36	38.8% (22.9–54.8%)	0.75
Non-PT regimens	18	44.4% (21.4–67.4%)	

PT Platinum/taxane

Most studies of salvage therapy have focused on the response to a particular single- or combined-drug regimen.

Table 4 Multivariate analysis of TTP and OS following third-line chemotherapy

Clinical factors	TTP *P* value	OS *P* value
Age (<60 vs. ≥60)	0.59	0.76
PS (0,1 vs. 2,3)	0.006	0.005
Pathology (mucinous/clear cell vs. non-mucinous/clear cell)	0.34	0.29
No. of target lesions (1 vs. 2,3)	0.85	0.79
Primary DFI (<6 months vs. ≥6 months)	0.01	0.004
Secondary DFI (<6 months vs. ≥ 6 months)	0.61	0.34
Response to second-line therapy (responder vs. non-responder)	0.43	0.17
PT regimens (PT regimens vs. non-PT regimens)	0.84	0.36

DFI Drug free-interval, *PT* Platinum/taxane

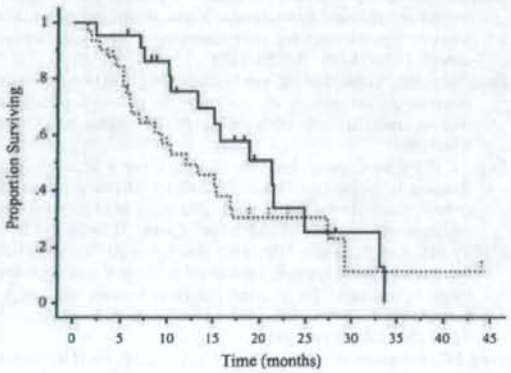

Fig. 3 Kaplan–Meier analysis of overall survival (*bottom*) following third-line chemotherapy. The difference between third-line responders (*solid line*) and third-line non-responders (*dotted line*) was not statistically significant ($P = 0.054$). *Vertical bars* indicate censored cases

Without well-designed controlled studies, however, it is difficult to determine outcomes that would be obtained if a drug were used earlier or later in the course of salvage treatment.

In our study, the RR to third-line chemotherapy was 40.7% (95% CI; 27.6–53.8%). To date, only a few authors have distinguished between second- and third-line treatments when evaluating drug response and survival rates. In a study by Villa et al. (1999), 49 patients with recurrent ovarian cancer received third-line drugs after complete or partial responses to second-line chemotherapy. The overall RR was 48%, and median survival was 6 months. The 1-year survival rate differed significantly between patients who responded and those who did not respond to second-line treatment (82 vs. 39%, $P < 0.05$).

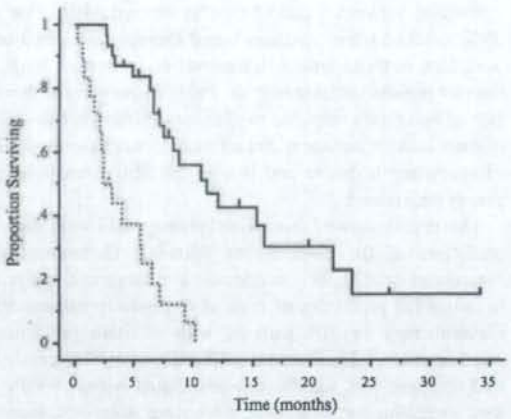

Fig. 4 Kaplan–Meier analysis of overall survival following fourth-line chemotherapy. The chemotherapy group (*solid line*) had significantly better survival ($P < 0.0001$) than the non-chemotherapy group (*dotted line*). *Vertical bars* indicate censored cases

We obtained good RRs to third-line treatment in patients with a good PS and those with a primary DFI of >6 months. The response to third-line chemotherapy is influenced by the response to second-line chemotherapy. However, third-line chemotherapy has only a modest RR with a marginal prolongation of progression-free interval, but no obvious effect on survival in patients with ovarian cancer (Tangjitgamol et al. 2004).

In our study, there was no significant difference in the survival rate between patients responded to third-line chemotherapy and those who did not. In terms of cost-effectiveness, best supportive care is the only cost-effective strategy, followed perhaps by second-line monotherapy, given currently available chemotherapeutic options (Rocconi et al. 2006).

Patients with recurrent disease are often retreated with the same primary drug(s), most often platinum agents, but might also receive other drugs (Markman et al. 1991; Thigpen et al. 1993; Bookman 2003; Fung et al. 2002). One of the most important considerations in selecting second-line therapy is platinum sensitivity status, as defined by the response of the primary disease to a platinum drug and the progression-free interval after the completion of treatment (Blackledge et al. 1989; Thigpen et al. 1993; Thigpen et al. 1994). Some researchers have argued that there is no definite treatment-free interval, which can reliably distinguish platinum sensitivity from platinum resistance (Markman 1998; Markman et al. 1998). Nonetheless, it is generally accepted that the longer the treatment-free interval, the better is the expected response to retreatment (Markman et al. 1991; Thigpen et al. 1994). One study reported that women with recurrent ovarian cancer who had a treatment-free

interval of between 5 and 12 months showed a RR of only 27% to second-line platinum-based therapy, as compared with 59% in those with a treatment-free interval of longer than 24 months (Markman et al. 1991). However, the duration of secondary response to platinum therapy is less well documented; in particular, the relation between the duration of secondary response and that of the initial response is poorly understood.

Our results showed that PS and primary DFI were useful predictors of the response to third-line chemotherapy. Eisenhauer et al. (1997) conducted a multivariate analysis to determine predictors of clinical response to subsequent chemotherapy in 704 patients with platinum-pretreated ovarian cancer. Their initial univariate analysis revealed that response was significantly associated with many factors, including the drug used, time since diagnosis, tumor size, histology, and the presence or absence of liver metastasis. In contrast, their multivariate analysis showed that only serous histologic type, number of disease sites ≤ 2, and maximum size of the largest lesion <5 cm were associated with a favorable response. They concluded that drug activity might not be the only determinant of response, and that tumor characteristics are also important factors.

In our study, two patients had hypersensitivity reactions to carboplatin. Patients who receive multiple courses of carboplatin have increased rates of hypersensitivity reactions (Zanotti et al. 2001). The incidence of such reactions is 27% in patients receiving 7 or more cycles of carboplatin, with more moderate to severe symptoms developing in more than 50% of these patients (Markman et al. 1999).

The time to treatment failure (4.4 months) and the OS (10.4 months) in our study were consistent with those reported by other studies assessing individual drugs (Villa et al. 1999; Heintz et al. 2001; Tangjitgamol et al. 2004; Rocconi et al. 2006). The survival of patients given fourth-line and subsequent treatment was significantly longer than that of patients who received no further therapy after third-line treatment (8.3 months vs. 2.4 months, respectively; $P < 0.0001$). Administration of fourth-line chemotherapy to patients who might tolerate such treatment may also improve OS; however, the analysis of OS in this setting has its limitations and is prone to potential bias. One study reported that giving additional lines of chemotherapy may not improve OS and that the inclusion of paclitaxel in treatment regimens may have a significant effect on survival (Findley et al. 2005).

In conclusion, our study suggested that PS and primary DFI may be useful predictors of the response to third-line chemotherapy in women with recurrent ovarian, fallopian tube, and primary peritoneal cancer. Our findings will hopefully help physicians make treatment recommendations and inform patients about expected benefits and risks, outcomes, and survival rates in this setting. Finally, the decision whether to use third-line chemotherapy should be based on a comprehensive assessment of patients' wishes, drug efficacy and toxicity, and treatment expertise of the clinician.

Acknowledgments This work was supported by The Supporting Fund of Obstetrics and Gynecology Kurume University.

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Lung Cancer (2008) 61, 350–355

available at www.sciencedirect.com

journal homepage: www.elsevier.com/locate/lungcan

Utility of ^{18}FDG-PET for differentiating the grade of malignancy in thymic epithelial tumors

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Received 14 August 2007; received in revised form 4 January 2008; accepted 11 January 2008

KEYWORDS
Thymic epithelial tumors;
Thymoma;
WHO histological classification;
PET;
^{18}F-FDG;
Thymic carcinoma

Summary
Purpose: The objective of this study was to assess the value of ^{18}F-FDG PET in thymic epithelial tumors according to the WHO histologic classification and to evaluate its potential for differentiating the grade of malignancy in thymic epithelial tumors.
Materials and methods: Thirty-six patients with a thymic epithelial tumor who underwent ^{18}F-FDG PET examination before treatment were enrolled in the present study. The T/M ratio, which is the ratio of the peak standardized uptake value (SUV) of the tumor to the mean SUV of mediastinum, was compared in subgroups of a simplified WHO histological classification; low-risk thymoma (Types A, AB and B1), high-risk thymoma (Types B2 and B3), and thymic carcinoma.
Results: Tumors included 15 low-risk thymomas, 10 high-risk thymomas and 11 thymic carcinomas. Upon visual inspection, all tumors showed ^{18}F-FDG accumulation and the mean T/M ratio in these three subgroups was 2.64, 4.29 and 8.90, respectively. The differences between the three subgroups were statistically significant (low-risk vs. high-risk: $p = 0.01$, high-risk vs. thymic carcinoma: $p = 0.01$).
Conclusion: A significant relationship was seen between ^{18}F-FDG PET accumulation and histologic subtype in thymic epithelial tumors when they were classified into three groups. PET may be useful for predicting the grade of malignancy in thymic epithelial tumors.

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doi:10.1016/j.lungcan.2008.01.003

1. Introduction

Among the tumors that originate in the thymus gland and involve the anterior mediastinum, thymic epithelial tumors are the most common. According to the extent of tumor growth, thymoma is classified as either a non-invasive type that is encased in a capsule or an invasive type, in which invasion occurs beyond the capsule [1]. Additionally, Masaoka's classification has also been widely used as a staging system for thymoma [16]. These classifications for tumor invasiveness have been the only important prognostic determinant for a long time.

In 1999, the World Health Organization (WHO) proposed a new histological classification (subsequently revised in 2004) for thymic epithelial tumors [2,3]. According to this classification, thymoma is classified as Types A, AB, B1, B2 or B3 based on the morphology and atypia of tumor epithelial cells. Since then, many studies have shown that this histological classification constituted an independent prognostic factor as well as a staging system [4–7,17,18]. In addition, the literature contains not only reports on conventional diagnosis based on tumor spreading, but also those on computed tomography (CT) and MRI findings of these tumors according to the WHO classification [8–11]. However, CT and MRI findings are still not entirely adequate for determining the histologic subtype of the WHO classification.

^{18}F-FDG PET examination reflects glucose metabolism in a tumor and is believed to serve as an indicator of tumor malignancy. While several studies have evaluated ^{18}F-FDG PET findings in thymic epithelial tumors [12–14], there have been few reports on both the WHO classification and ^{18}F-FDG PET of thymic epithelial tumors [15].

If we could predict the grade of malignancy of thymic epithelial tumors to some extent, useful information would be available for the staging diagnosis offered by CT and MRI before treatment.

To clarify the possibility of differentiating the grade of malignancy in thymic epithelial tumors by PET, we estimated the relationship between the WHO histologic subtype and ^{18}F-FDG accumulation in the tumor.

2. Materials and methods

2.1. Patients

This study group consisted of 36 consecutive patients (21 men and 15 women, age range 32–80 years; mean 59.1) with histologically proven thymic epithelial tumor treated in our institution between October 2002 and September 2006. Twenty-one cases were diagnosed by surgical excision and 15 cases were diagnosed by percutaneous coreneedle biopsy. All patients underwent chest radiography, contrast-enhanced computed tomography, and ^{18}F-FDG PET to determine the clinical stage before treatment. Several patients also underwent MRI. All patients were enrolled after they gave their written informed consent in accordance with the regulations of the institutional review board.

2.2. ^{18}F-FDG-PET imaging

Patients fasted for at least 4 h before ^{18}F-FDG PET examination. Patients received an intravenous injection of 200–250 MBq of [18] fluoro-2-deoxy-D-glucose and then rested for approximately 1 h before undergoing imaging. Image acquisition was performed using an Advance NXi PET scanner and Discovery PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). Two-dimensional emission scanning was performed from the groin to the top of the skull. Acquired data were reconstructed by iterative ordered subset expectation maximization. To evaluate ^{18}F-FDG accumulation, the tumor was first examined visually, and then the peak standardized uptake value (SUV) of the entire tumor was determined. The region of interest (ROI), measuring 3 cm in diameter, was set at the mediastinum at the level of the aortic arch and the mean SUV of the mediastinum was calculated. Finally, the T/M ratio, which is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum, was determined for each patient.

2.3. Clinical Stage

Masaoka's classification [16] was used for staging in all patients. For patients with surgical excision, the stage was determined by operative and pathological findings. In contrast, for patients with biopsy only, the stage was determined by diagnostic imagings including CT, MRI and FDG-PET.

2.4. Pathological diagnosis

For patients who had undergone surgery, the WHO histological classification was determined by surgically excised specimens. For those without surgery, the histological classification was determined by specimens obtained through coreneedle biopsy. We divided five WHO histologic subtypes of thymoma into two subgroups as follows; low-risk thymoma (Types A, AB and B1) and high-risk thymoma (Types B2 and B3).

2.5. Statistical analysis

The mean and standard deviation of the T/M ratio were calculated. These data were compared among low-risk thymoma, high-risk thymoma and thymic carcinoma. The statistical differences of the T/M ratios between the three subgroups of thymic epithelial tumors were analyzed by the Chi-square test. A P-value of less than .05 was considered to be statistically significant.

3. Results

Both CT and PET images of each histologic subtype are shown in Figs. 1–5. According to the simplified subgroups of the WHO classification, the tumors included 15 low-risk thymomas (2 Type A, 8 Type AB and 5 Type B1), 10 high-risk thymomas (4 Type B2 and 6 Type B3) and 11 thymic carcinomas. Upon visual inspection, all tumors showed ^{18}F-FDG accumulation. As shown in Table 1 and Fig. 6, the T/M ratio was 2.64 ± 0.78 (mean, S.D., range: 1.52–4.68), 4.29 ± 1.41 (2.60–6.64) and 8.90 ± 3.62 (4.47–18.73), respectively, with significant differences between the three groups (low-risk vs. high-risk: $p = 0.01$, high-risk vs. thymic carcinoma: $p = 0.01$).

Fig. 1 A 55-year-old woman with Type A in Masaoka stage I. CT showed a clear demarcation at the anterior mediastinum and an evident tumor outline in the internal wall structure. The ^{18}F-FDG PET examination showed that ^{18}F-FDG accumulation in the tumor was slightly more pronounced than that in the mediastinum. The T/M ratio was 2.12.

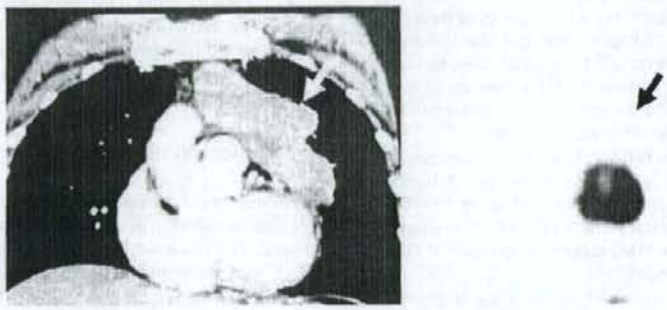

Fig. 2 A 58-year-old woman with Type B1 in Masaoka stage IVa. An irregular-shaped tumor with an uneven margin was found projecting to the left side of the anterior mediastinum. CT also indicated tumor dissemination, which suggested malignancy that exceed that of a high-risk thymoma, but ^{18}F-FDG accumulation in the tumor was similar to that in the mediastinum, with a T/M ratio of 1.70. This was thought to be a low-risk thymoma.

According to Masaoka's classification, among the 15 patients with low-risk thymoma, 6 were in stage I, 6 in stage II, 2 in stage III and 1 in stage IV. Among the 10 patients with high-risk thymoma, 2 were in stage I, 1 in stage II, 5 in stage III and 2 in stage IV. In contrast, among the 11 patients with thymic carcinomas, three were in stage III and 8 in stage IV. Among the 15 patients with biopsy only, 4 were in stage III and 11 were in stage IV.

Fig. 3 A 40-year-old man with Type B2 and Masaoka stage II. CT revealed that the tumor morphology was similar to that in Fig. 2, but ^{18}F-FDG PET showed that ^{18}F-FDG accumulation in the tumor was more pronounced than that in the mediastinum. The T/M ratio was 3.40.

Fig. 4 A 41-year-old man with Type B3 in Masaoka stage III. CT detected a round tumor with a slightly irregular border that projected to the left side of the anterior mediastinum. It was suggested that the tumor was perhaps a low-risk thymoma. However, ^{18}F-FDG PET showed accentuated ^{18}F-FDG accumulation in the tumor. The T/M ratio was 6.14. This was thought to be a high-risk thymoma.

Fig. 5 A 56-year-old man with thymic carcinoma in Masaoka stage IV. CT showed a tumor with an irregular border that occupied the anterior mediastinum. Tumor dissemination to the pleura was also noted. ^{18}F-FDG PET showed accentuated ^{18}F-FDG accumulation not only in the tumor but also in tumor dissemination. The T/M ratio was 9.65.

Table 1 T/M ratios of subgroups in a simplified WHO classification

WHO classification	Number of patients	T/M ratio (S.D.)
A	2	
AB	8	2.64 ± 0.78
B1	5	
B2	4	4.29 ± 1.41
B3	6	
Thymic carcinoma	11	8.90 ± 3.62

4. Discussion

There are several reports on ^{18}F-FDG PET examinations for thymus-originated tumors. Liu et al. stated that ^{18}F-FDG accumulation was not related to Masaoka's classification in thymoma, but PET diagnosed tumor invasiveness more accurately than CT or MRI [12]. Kubota et al. stated that ^{18}F-FDG accumulation in thymoma was evidently greater than that in benign lesions and this accumulation was particularly pronounced in invasive thymoma or thymic carcinoma and was at an intermediate level in non-invasive thymoma [13]. Thus, though several reports have described PET findings in thymic epithelial tumor, its clinical significance is still unclear.

With regard to the histological classification, the WHO histological classification of thymic epithelial tumors was established for the first time in 1999 [2]. According to this classification, thymomas were classified as Type A or B according to their epithelial cell morphology. Type B thymomas were further subdivided into B1 to B3 according to the atypia of epithelial cells and the extent of lymphocyte infiltration. The co-existence of both Types A and B was designated Type AB. In addition, thymic carcinoma was added as Type C thymoma. The revision made in 2004 eliminated the term Type C thymoma and defined thymic carcinoma, including neuroendocrine epithelial tumors of the thymus, as an independent entity. To date, many studies on the significance of the WHO histological classification have demonstrated that it is an independent prognostic factor, as is Masaoka's classification [4–7,17,18].

Recently, several authors attempted to establish a simpler version of the WHO classification. Chen et al. stated that the WHO classification constituted an independent

Fig. 6 T/M ratios in subgroups of a simplified WHO classification. The T/M ratio was 2.64 ± 0.78 (mean, S.D., range: 1.52–4.68), 4.29 ± 1.41 (2.60–6.64) and 8.90 ± 3.62 (4.47–18.73), respectively, with significant differences between the three groups (low-risk vs. high-risk: $p = 0.01$, high-risk vs. thymic carcinoma: $p = 0.01$).

prognostic factor when Type A-B1 thymomas were grouped as low-risk and Type B2-C thymomas were grouped as high-risk [6]. Okumura et al. reported that the WHO classification together with the Masaoka classification constituted independent prognostic factors, and that Type B2 or B3 thymoma was associated with a particularly high recurrence rate and a worse prognosis [5]. Jeong et al. stratified thymic epithelial tumors roughly into three subgroups based on their prognosis and according to the WHO classification (Type A-B1, low-risk thymoma; B2-3, high-risk thymoma and thymic carcinoma) and reported the possibility of a CT diagnosis for these three subgroups [9]. They stated that CT and/or MR imaging findings are helpful for differentiating low-risk and high-risk thymomas from thymic carcinomas. Sadohara et al. also attempted to differentiate these three subgroups by CT and MRI based on a proposal by Jeong et al. [9]. Although this simplified classification has not yet been fully discussed worldwide [17,18], in our present study we focused on a comparison of ^{18}F-FDG accumulation in the three subgroups of this simplified WHO classification, as done by Sung et al. in their study [15].

Accumulation was noted in all of the thymic epithelial tumors. For low-risk thymoma, accumulation was only about 2.5 times higher than that in the mediastinum. In contrast, it was about 4.3 times higher in high-risk thymomas and about nine times higher in thymic carcinomas. The degree of ^{18}F-FDG accumulation in tumors when stratified by the T/M ratio differed significantly between these three groups. Our results suggested that PET was helpful in differentiating these three subgroups. Although our study did not include an evaluation of the prognosis, the results suggested that FDG-PET may reflect the grade of malignancy in thymic epithelial tumors based on a consideration of several studies on the prognostic significance of the WHO classification [4–7,17,18]. Thus, ^{18}F-FDG PET may enable us to determine the grade of malignancy in thymic epithelial tumors and offers useful information to aid in CT and MRI diagnoses.

The degree of ^{18}F-FDG accumulation becomes increasingly more accentuated as the classification shifts from Type A to Type B and eventually to thymic carcinoma. Meanwhile, the amount of lymphocyte infiltration in the tumor gradually decreased from Type B1 to Type B3. From a pathological point of view, ^{18}F-FDG accumulation in the tumor may not be affected by the amount of lymphocytes but rather is mainly affected by the degree of atypia of epithelial cells.

In this study, we did not evaluate Masaoka's classification in detail. Further studies on the relationship between ^{18}F-FDG PET accumulation and Masaoka's classification should be conducted in a sufficient number of patients.

The current study has the following limitations: (1) two types of PET scanner were used and the dosage for ^{18}F-FDG was not uniform; (2) not all pathological diagnoses were derived from surgical specimens, and biopsy specimens were used in some cases; (3) contrast and evaluation of CT and MRI were not conducted; (4) the observation period was short and a prognostic evaluation was not done.

5. Conclusion

^{18}F-FDG PET accumulation in thymic epithelial tumors significantly correlated with a simplified WHO classification. These findings suggest that PET reflected the grade of malignancy in thymic epithelial tumors and was helpful in differential diagnosis according to the WHO classification. This diagnostic procedure may play an important role in the diagnosis of thymic epithelial tumors in the near future.

Conflict of interest

None.

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Jpn J Clin Oncol 2008;38(3)214–221
doi:10.1093/jjco/hyn002

Weekly Epoetin Beta Maintains Haemoglobin Levels and Improves Quality of Life in Patients with Non-Myeloid Malignancies Receiving Chemotherapy

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Received July 23, 2007; accepted December 28, 2007; published online February 21, 2008

Objective: This study was aimed at investigating the effectiveness and safety of once-weekly epoetin beta for anaemic cancer patients receiving chemotherapy.
Methods: A total of 104 patients with a haemoglobin level of ≤11.0 g/dL were enrolled. Patients received a once-weekly subcutaneous dose of 36 000 IU epoetin beta for 12 weeks. If the increase in the haemoglobin level was <1.0 g/dL after 6 weeks, or a red blood cell transfusion was required between days 15 and 42, the dose of epoetin beta was increased to 54 000 IU from the subsequent week. The primary endpoint was the percentage of patients who achieved a haemoglobin increase of ≥2.0 g/dL; the haemoglobin response rate. Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire.
Results: The haemoglobin response rate was 66.3% among the 98 patients (breast cancer: $n = 25$; malignant lymphoma: $n = 21$; ovarian cancer: $n = 20$; lung cancer: $n = 15$; other cancers: $n = 17$) assessable for a haemoglobin response. Thirty-nine patients (39.8%) required a dose escalation to 54 000 IU. At the end of the study, QOL assessable patients ($n = 96$) showed a mean improvement in the FACT-An total fatigue subscale score (FSS) of 0.3 points from baseline. Patients with a haemoglobin response had a mean change in the total FSS of +3.2, compared with −3.4 for patients without a haemoglobin response. No serious adverse event of epoetin beta was observed.
Conclusions: Epoetin beta administered at an initial dose of 36 000 IU once-weekly was well tolerated, with increased haemoglobin levels and improved QOL in anaemic cancer patients receiving myelosuppressive chemotherapy.

Key words: anaemia – erythropoietin – cancer – chemotherapy – quality of life

INTRODUCTION

Anaemia is a common complication of cancer patients undergoing chemotherapy. Symptoms of anaemia, including fatigue, palpitations, dizziness and dyspnea markedly reduce patient activity, resulting in impaired quality of life (QOL). In most cases, however, physicians hesitate to prescribe red blood cell (RBC) transfusions until the haemoglobin level is <8.0 g/dL, even if the patient has symptoms related to anaemia, such as fatigue. Although the safety of blood transfusion has improved in recent years, risks still remain, such as viral infections, graft versus host disease and haemolytic reactions.

In Europe and the United States, erythropoietin (EPO) agents have widely been used since the 1990s for the treatment of chemotherapy-induced anaemia. Although a three-times weekly dosing schedule was initially introduced (1–3), this schedule was inconvenient for outpatients. Several studies reported that once-weekly dosing of EPO increased the

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haemoglobin level and improved QOL in a manner comparable with those obtained by three-times weekly dosing (4,5).

Since EPO agents have not been approved for the treatment of chemotherapy-induced anaemia in Japan, we previously conducted a dose-finding study of weekly epoetin beta in patients with malignant lymphoma or lung cancer, resulting in a recommended weekly dose of 36 000 IU (6). In this prospective study, we investigated the haemoglobin response, the effects on QOL and the safety of once-weekly epoetin beta in anaemic patients with non-myeloid malignancies. We also investigated the effects of dose escalation to 54 000 IU in patients showing insufficient haemoglobin increase.

PATIENTS AND METHODS

Patient Eligibility

Inclusion criteria were as follows: (a) histological or cytological confirmation of non-myeloid malignancy diagnosis, (b) treatment with cyclic chemotherapy, (c) anaemia (haemoglobin level $\leq$11.0 g/dL) considered to be primarily chemotherapy-induced, (d) life expectancy of at least 4 months, (e) aged between 20 and 79 years, (f) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, (g) eligibility for the QOL questionnaire and (h) adequate hepatic and renal function.

Exclusion criteria included: (a) iron deficiency (mean corpuscular volume $<80\ \mu m^3$ or iron saturation [{Fe/(Fe+unsaturated iron-binding capacity)} $\times$ 100] $<$15.0%); (b) surgery scheduled during the study period; (c) EPO therapy within 4 weeks prior to the study; (d) documented haemorrhagic lesions; (e) pregnancy, breastfeeding or non-use of adequate birth control measures; (f) history of myocardial, pulmonary, cerebral infarction, serious drug allergy, uncontrolled hypertension, hypersensitivity to any EPO agent or any serious complication; and (g) tumor in the central nervous system.

Study Design and Treatment Schedule

This multicentre, open-label study was conducted at 14 sites in Japan.

The protocol was approved by the institutional review board of the respective hospitals, and written informed consent was obtained from all patients who participated in the study.

The initial dose of epoetin beta (Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) was 36 000 IU, and a once-weekly treatment was administered subcutaneously for 12 weeks. If the patient's haemoglobin level did not increase by $\geq$1.0 g/dL from baseline after 6 weeks of treatment, or an RBC transfusion was required between days 15 and 42, the dose of epoetin beta was increased to 54 000 IU weekly from the subsequent week. If the haemoglobin level increased to $\geq$14.0 g/dL, epoetin beta was discontinued until the haemoglobin level decreased to $\leq$12.0 g/dL, and was then restarted at two-thirds (24 000 IU or 36 000 IU) of the previous dose (36 000 IU or 54 000 IU). RBC transfusion was allowed at the discretion of the investigator during the study. An oral daily dose of 100–200 mg elemental iron was recommended if the mean corpuscular volume was $<80\ \mu m^3$ or the iron saturation was $<$15.0%.

QOL was evaluated at baseline and week 12 using the Japanese Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire (7,8), a well-validated instrument. In this study, the FACT-An total fatigue subscale, which consists of 13 fatigue related questions, was mainly analysed. The FACT-An total fatigue subscale scores (FSS) range from 0 to 52, with higher scores indicating less fatigue.

Evaluation of Efficacy and Safety

The American Society of Clinical Oncology/The American Society of Hematology guidelines (9) stipulate that the criteria for the haemopoietic effect should be an increase in haemoglobin level $\geq$1.0–2.0 g/dL in 6–8 weeks. Furthermore, there are reports (2,6), which showed that QOL is improved in patients with an increase in haemoglobin level of $\geq$2.0 g/dL.

The primary endpoint of the study was the percentage of patients achieving an increase in the haemoglobin level of $\geq$2.0 g/dL from the baseline between weeks 4 and 12, the haemoglobin response rate, excluding the data within 28 days after an RBC transfusion. The secondary endpoint was the change in FSS after 12 weeks of treatment. The percentage of patients receiving RBC transfusions between day 28 and the end of the study was also assessed. It was not expected that treatment with an EPO agent could influence transfusion requirements before day 28.

Adverse events (AEs) were assessed during the 12-week treatment period and during a 1-week observation period after the last dosing. Anti-erythropoietin antibodies were measured by the enzyme-linked immunosorbent assay and radio-immunoprecipitation (RIP) assay, and detection by either was judged as positive.

Statistical Analysis

We expected that 90 patients would need to be enrolled in the study to obtain a haemoglobin response rate of 70 $\pm$ 10% (95% confidence interval [CI]), as the primary endpoint.

Patients who received at least one dose of the study drug comprised the safety population. For efficacy analysis, the full analysis set (FAS) population was defined as eligible patients who received at least one dose of the study drug.

The changes in the haemoglobin level and FACT-An scores were calculated by subtracting each patient's baseline values from the last values. The rates of increase in haemoglobin before and after dose escalation were compared using a linear mixed-effects model. The potential factors influencing the change in FSS were examined by multiple

regression analysis. Pearson correlation coefficients were calculated to assess the association between changes in the haemoglobin level and FACT-An scores.

RESULTS

Demographics and Baseline Characteristics

A total of 104 patients were enrolled in the study between February and November 2004. Five patients discontinued the study before the first dosing for the following reasons: patient eligibility criteria violation, $n = 3$; patient denial, $n = 1$; and disease progression, $n = 1$. Thus, 99 patients were administered epoetin beta. One patient was excluded because of non-compliance with the eligibility criteria, leaving 98 patients as the FAS population. Eighty-seven patients (88.8%) completed all 12 weeks of the study. Eleven patients (11.2%) withdrew from the study. The primary reasons for withdrawal were progressive disease and AEs.

The demographics and baseline characteristics of the FAS population are listed in Table 1. Common types of cancer were breast ($n = 25$), malignant lymphoma ($n = 21$), ovarian ($n = 20$) and lung ($n = 15$). The mean age was 58.4 years (range: 23–78), and the mean body weight was 50.7 kg (range: 31.7–74.0). Most of the patients had an ECOG PS of 0 or 1 and a tumour stage of III or IV. The main chemotherapeutic agents used during the study were platinum for lung and other types of cancer, anthracycline for malignant lymphoma, taxane for breast cancer and platinum plus taxane for ovarian cancer. All patients met the criterion that they should not be iron-deficient at the time of enrollment.

Haemoglobin Response

The mean change in the haemoglobin level from baseline to the end of the study was 2.47 g/dL (standard deviation [SD]: 2.09; range: −2.8 to 6.0), as shown in Fig. 1. Figure 1 shows the mean changes in haemoglobin levels by tumour type. The pattern of changes in haemoglobin level was similar for the different tumour types. The mean increase in the haemoglobin level in patients with and without an initial EPO level of ≥100 mIU/mL were 1.76 g/dL (SD: 2.60) and 2.50 g/dL (SD: 1.85), respectively.

The haemoglobin response rates, defined as the percentage of patients achieving an increase in haemoglobin level of ≥2.0 g/dL from the baseline between weeks 4 and 12, are listed in Table 2. The overall haemoglobin response rate was 66.3% (65 of 98 patients). The median time to the haemoglobin response was 56 days from the first dosing, analysed by the Kaplan–Meier method. The percentage of patients with a haemoglobin level of ≥12.0 g/dL between weeks 4 and 12 was 59.2% (58 of 98 patients).

The percentage of patients who required dose escalation to 54 000 IU was 39.8% (39 of 98 patients). In these patients, the haemoglobin level increased after dose escalation, and the change in the haemoglobin level was 1.23 g/dL (SD: 2.19) at the end of the study. The haemoglobin response rate was 33.3% (13 of 39 patients) in patients who required dose escalation. The rate of haemoglobin increase before and after dose escalation was 0.023 g/dL/week (Weeks 0–6) and 0.266 g/dL/week (Weeks 7–12), respectively ($P = 0.0055$).

For three patients, the drug treatment was discontinued when the haemoglobin level exceeded 14.0 g/dL, and was restarted at a dose of 24 000 IU when the haemoglobin level decreased to ≤12.0 g/dL.

Quality of Life

Overall compliance in terms of the percentage of patients who completed the FACT-An was 100% at baseline and 97% (95 of 98 patients) at the end of the study. For three patients who dropped out due to progressive disease and were regarded as missing not at random, the scores at the end of the study were substituted with the minimum scores for all patients. Two patients were excluded from the evaluation of the change in the FSS because the responses to some items were missing.

The mean baseline FSS was 31.8 (SD: 11.4, $n = 98$) points. At the end of the study, the mean change from baseline was 0.3 (SD: 11.8, $n = 96$) points. The mean FSS change in the patients with progressive disease, as judged by each investigator, was −3.8 (SD: 16.7, $n = 15$) points (haemoglobin change: 2.4 g/dL). On the other hand, the mean change in patients without progressive disease was 1.9 (SD: 9.6, $n = 78$) points (haemoglobin change: 2.3 g/dL). These data indicated that progressive disease may be one of the independent variables affecting the change in FSS.

Relationship Between Haemoglobin Response and QOL Score

The results of a multiple regression analysis suggested that the change in the haemoglobin level ($P = 0.014$), the FSS at the initiation of dosing ($P < 0.0001$) and the PS at the end of the study ($P < 0.0001$) largely contributed to the change in the FSS. The correlation coefficient between the change in the FSS and the changes in the haemoglobin level was 0.280, indicating a significant correlation ($P = 0.006$, $n = 96$).

Patients who achieved an increase in the haemoglobin level of ≥2.0 g/dL experienced a 3.2-point mean change in FSS. On the other hand, patients who did not achieve an increase in haemoglobin level of ≥2.0 g/dL experienced a −3.4-point change (Fig. 2). There were no differences in the FSS at the initiation of dosing between patients with and without a change in haemoglobin level of ≥2.0 g/dL (32.0 versus 31.6). These data indicate that the change in FSS is dependent on the change in the haemoglobin level.

Concerning the relationship between the FSS at the initiation of dosing and the change in the FSS, patients with a baseline FSS of ≤36.0 reported greater improvement (mean ± SD: 1.6 ± 13.0) in the FSS at the end of the study (Table 3).

Table 1. Characteristics of the full analysis set population

	Characteristics	Total	Lung	Malignant Lymphoma	Breast	Ovarian	Other types
Sex	Male	27	11	10	0	0	6
	Female	71	4	11	25	20	11
Age (years)	Mean ± SD	58.4 ± 10.8	60.5 ± 10.5	56.5 ± 13.4	58.2 ± 9.0	54.4 ± 11.0	63.8 ± 8.0
	Range	23–78	41–78	23–74	39–77	30–75	40–76
ECOG performance status	0	48	1	9	14	13	11
	1	39	12	9	6	6	6
	2	11	2	3	5	1	0
Tumour stage	I	6	0	1	3	2	0
	II	17	1	4	7	4	1
	III	15	0	3	0	9	3
	IIIA	2	1	0	1	0	0
	IIIB	8	6	0	2	0	0
	IV	50	7	13	12	3	13
Treatment regimen	Platinum based	17	7	2	0	1	7
	Taxane based	28	5	0	19	3	1
	Anthracycline based	28	1	18	6	0	3
	Platinum, Anthracycline based	4	0	1	0	1	2
	Platinum,Taxane based	21	2	0	0	15	4
Weight (kg)	Mean ± SD	50.7 ± 8.2	53.8 ± 8.7	52.7 ± 9.9	47.9 ± 7.2	49.3 ± 6.6	50.9 ± 7.4
	Range	31.7–74.0	38.0–70.7	31.7–74.0	34.0–63.0	34.1–60.0	37.7–65.5
Haemoglobin (g/dL)	Mean ± SD	9.3 ± 1.4	9.6 ± 1.4	9.3 ± 1.4	9.4 ± 1.4	9.2 ± 1.6	9.1 ± 1.4
	Range	5.6–11.9	6.4–11.2	6.5–11.3	5.7–11.9	6.4–11.7	5.6–11.1
MCV (fL)	Mean ± SD	92.3 ± 6.5	89.0 ± 6.4	90.0 ± 5.4	91.9 ± 5.6	94.6 ± 7.5	95.7 ± 5.3
	Range	79.9–107.5	79.9–99.3	80–101	80.5–103.2	81.9–107.5	84–103.4
Reticulocyte (‰)	Mean ± SD	19.7 ± 16.4	20.8 ± 15.1	24.2 ± 24.1	18.0 ± 13.2	21.1 ± 15.6	14.1 ± 10.3
	Range	1–106	2–50	1–106	1–58	1–54	1.1–35.1
Transferrin saturation (%)	Mean ± SD	29.7 ± 22.3	22.4 ± 7.1	41.5 ± 30.6	21.9 ± 16.9	31.1 ± 24.3	30.5 ± 18.0
	Range	4.8–92.9	12.5–35.5	9.9–92.9	4.8–80.6	7.2–90.7	14.0–90.3
Serum endogenous erythropoietin (mIU/mL)	Mean ± SD	119.1 ± 310.5	64.5 ± 69.9	80.7 ± 108.0	88.4 ± 107.1	125.9 ± 144.8	282.0 ± 706.0
	Range	15.7–2970	15.7–234	17.5–399	16.7–472	23.2–578	20.4–2970
Baseline QOL FACT-An							
Anemia subscale (0–80)	Mean ± SD	50.8 ± 14.5	47.0 ± 15.9	50.6 ± 11.7	47.1 ± 13.7	53.5 ± 11.1	58.7 ± 19.5
	Range	16–80	17–74	26–67	20–71	34–75	16–80
Fatigue subscale (0–52)	Mean ± SD	31.8 ± 11.4	29.6 ± 12.9	30.3 ± 10.6	29.7 ± 10.7	33.9 ± 8.7	36.5 ± 14.1
	Range	4–52	4–52	10–43	7–50	20–48	8–52

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; QOL, quality of life; FACT-An, Functional Assessment of Cancer Therapy-Anemia; MCV, mean corpuscular volume.

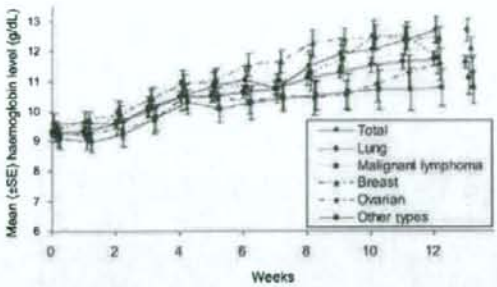

Figure 1. Change in haemoglobin level by tumor type. Mean weekly haemoglobin levels for the FAS population. Haemoglobin values within 28 days after RBC transfusion were excluded. FAS, full analysis set; RBC, red blood cell.

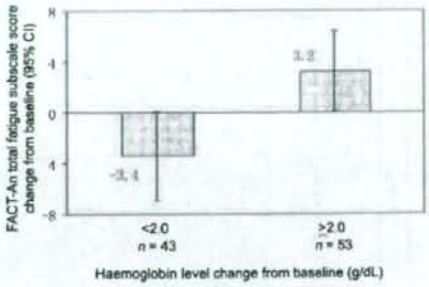

Figure 2. Changes in the FACT-An total fatigue subscale score by change in haemoglobin level. FACT-An, Functional Assessment of Cancer Therapy-Anaemia.

RBC Transfusion Requirement

The percentage of patients who received RBC transfusions between day 28 and the end of the study was only 6.1% (6 of 98 patients). The mean pretransfusion haemoglobin level at the time of the first transfusion was 6.2 g/dL (range: 5.4–7.3 g/dL). The percentage of patients whose haemoglobin level had decreased to <8.0 g/dL or who received an RBC transfusion between day 28 and the end of the study was 20.4% (20 of 98 patients).

Safety

AEs reported by at least 20% of the patients are summarised in Table 4. Death as a result of disease progression was not reported as an AE. Adverse drug reactions reported by at least 5% of patients are listed in Table 5. Among the 133 events in 48 patients (48.5%) that were considered related to the study drug, Grade III events were headache, hypertension, diarrhea, decreased serum potassium, impaired consciousness, anorexia and decreased serum phosphate. Three events (3.0%) of hypertension were reported as possibly related to epoetin beta treatment. An antihypertensive drug was administered after the onset of hypertension in one patient, who had hypertension as a comorbidity before the study. One patient (65-year-old female with malignant lymphoma) experienced a thrombovascular event, a lacunar infarction, at week 6. This event was evaluated as being unrelated to epoetin beta and was attributed to aging.

The incidence and type of AEs in patients who required dose escalation did not differ from those in patients who did not.

In two patients with ovarian and gastric cancer, anti-erythropoietin antibodies were detected only by RIP assay.

Table 2. Haemoglobin response rate by baseline haemoglobin, tumour type and dose escalation

	%	*n*
Response rate*	66.3	65/98
Response rate by baseline haemoglobin, g/dL		
<10.0	68.8	44/64
≥10.0	61.8	21/34
Response rate by tumour type		
Lung	80.0	12/15
Malignant lymphoma	66.7	14/21
Breast	76.0	19/25
Ovarian	65.0	13/20
Other types	41.2	7/17
Response rate by dose escalation		
Yes	33.3	13/39
No	88.1	52/59

*All patients, including those receiving transfusions.

Table 3. Changes in the FACT-An total fatigue subscale score by baseline FSS and final PS

Time period	Baseline			End of treatment	
	n	Mean score (SD)	*n*	Mean score (SD)	Mean change from baseline (SD)
Total	98	31.8 (11.4)	96*	31.8 (13.5)	0.3 (11.8)
Baseline FSS					
≤36.0	62	24.8 (7.9)	62	26.5 (12.0)	1.6 (13.0)
>36.0	36	43.9 (4.0)	34*	41.5 (10.3)	−2.2 (8.8)
Final PS					
0	58	35.5 (11.3)	56*	37.4 (10.3)	2.4 (10.2)
1	28	27.4 (9.1)	28	29.0 (11.5)	1.6 (12.2)
2	4	19.3 (9.4)	4	11.8 (11.4)	−7.5 (7.9)
3	3	29.7 (15.9)	3	21.0 (7.2)	−8.7 (13.8)
4	5	25.7 (7.3)	5	6.4 (7.1)	−19.3 (6.4)

*Two patients missing FSS. Collected but could not be calculated.
FSS, FACT-An total fatigue subscale score; PS, performance status.

Table 4. Frequencies of adverse events ($n = 99$)

Event	n	%	Grade*				
			I	II	III	IV	V
Neutropenia	83	83.8	3	11	24	45	0
Leukopenia	78	78.8	2	16	41	19	0
Nausea	57	57.6	38	11	8	0	0
Thrombocytopenia	55	55.6	21	9	23	2	0
Lymphopenia	52	52.5	0	18	34	0	0
Anorexia	46	46.5	22	13	10	1	0
Fatigue	39	39.4	22	14	3	0	0
Vomiting	36	36.4	18	16	2	0	0
Diarrhea	33	33.3	23	6	4	0	0
Increased lactate dehydrogenase	32	32.3	25	6	1	0	0
Peripheral neuropathy	26	26.3	21	5	0	0	0
Fever	26	26.3	17	7	2	0	0
Constipation	24	24.2	3	13	7	1	0
Increased alanine aminotransferase	24	24.2	15	6	3	0	0
Alopecia	22	22.2	7	15	0	0	0

*National cancer institutes common toxicity criteria, version 2.0.

Table 5. Frequencies of adverse drug reactions ($n = 99$)

Event	n	%	Grade*				
			I	II	III	IV	V
Increased lactate dehydrogenase	10	10.1	9	1	0	0	0
Headache	7	7.1	6	0	1	0	0
Nausea	7	7.1	5	2	0	0	0
Rash	5	5.1	3	2	0	0	0
Back pain	5	5.1	5	0	0	0	0

*National cancer institutes common toxicity criteria, version 2.0.

Neutralisation of EPO activity was detected in neither patient, and the haemoglobin level was elevated after dosing with the study drug. The investigators judged that the antibody did not cause pure red cell aplasia.

When re-examined six months after the last observation, one of these patients (ovarian cancer) was antibody negative, whereas the other (gastric cancer) could not be re-examined, having died of the underlying disease.

DISCUSSION

Several studies have been conducted to assess the effects of EPO agents in anaemic cancer patients, and increased haemoglobin levels and improvement in QOL that correlated with the increased haemoglobin level were reported (1,10).

The objectives of our study were to investigate the effects of an initial once-weekly 36 000 IU dose of epoetin beta on haemoglobin levels and QOL in patients with non-myeloid malignancy undergoing chemotherapy. The criterion for a haemoglobin response, an increase in the haemoglobin level of $\geq$2.0 g/dL, was based on a report that symptoms of anaemia assessed by the FACT-An are improved in patients with a change in the haemoglobin level of $\geq$2.0 g/dL (2,6). According to this index, the haemoglobin response rate in the present study was 66.3% (65 of 98 patients). The increases in haemoglobin levels that were observed were independent of the tumour type or the baseline haemoglobin level. None of the investigators performed a randomised comparison of a dose increase versus an unchanged dose in EPO low responders. In the present study, there was an increase in the rate of haemoglobin increase after dose escalation to 54 000 IU, and the haemoglobin response rate for patients who required a dose escalation was 33.3% (13 of 39 patients).

The secondary endpoint, the change in the FSS, showed an increase of 0.3 points; however, in patients who showed an increase in the haemoglobin level of $\geq$2.0 g/dL, the FSS was increased by 3.2 points, which was significantly higher than the -3.4-point change in patients whose haemoglobin level increased by <2.0 g/dL. A 3.2-point increase is comparable with the 3 points considered to be a clinically significant change in FSS (11). In addition, the mean change in FSS for patients with progressive diseases (PD) was -3.8 points (median: -6.5 points, range: -37 to 35 points) even though correction of anaemia was observed. In total, excluding PD cases, a 1.9- point improvement was observed.

Investigating the relationship between the FSS at the initiation of dosing and the change in the FSS showed that greater improvements in FSS were observed in patients with lower FSS. The FSS before treatment with epoetin beta was 31.8 ± 11.4 points, which is higher than the scores (FSS: 22.1–29.7 points, change in FSS: 1.6–5.2 points) in cancer patients with anaemia reported in several randomised trials (1,10,12–14). Nevertheless, the mean initial haemoglobin level (9.3 g/dL) in the present study was equal to the levels in the other trials (9.2–10.1 g/dL). Since it has been reported that the FSS after treatment with an EPO agent is aggravated in patients with an FSS exceeding 36.0 at the initiation of dosing (15), the scores were analysed after stratification at 36.0. This resulted in improved scores (1.6 ± 13.0 points) for those patients with a baseline score of $\leq$36.0, when compared with patients with a score $>$36.0 (-2.2 ± 8.8 points). The results of a multiple regression analysis of the change in the FSS demonstrated that the change in the haemoglobin level, the FSS at the initiation of dosing and the PS at the end of the study were factors that largely contributed to the change in the FSS. A positive and significant association was observed between