Table I. Patient characteristics of 132 included and 49 excluded subjects upon diagnosis of HCV-LC.

Characteristics	Study included	Study excluded	*p*-value
No. of cases	132	47	
Age (years) (mean (SD))	59.0 (7.1)	57.2 (7.8)	0.138
Gender (M/F)	59/73	33/14	0.003*
BMI (mean (SD))	24.1 (3.0)	23.4 (3.3)	0.207
Smoking habit (+)/(−)	49/80	30/17	0.002*
Liver tests			
Albumin (g/dl)			
Mean (SD)	4.1 (1.2)	4.0 (0.5)	0.457**
Median (IQR)	3.9 (3.6–4.3)	4.0 (3.6–4.3)	
ASAT (IU)			
Mean (SD)	94.7 (50.3)	109.8 (81.1)	0.506**
Median (IQR)	86.0 (60.3–124.3)	87.0 (57.8–142.3)	
ALAT (IU)			
Mean (SD)	108.9 (64.1)	108.6 (63.3)	0.937**
Median (IQR)	94.0 (64.0–139.8)	101.0 (60.0–160.0)	
Prothrombin time (%)			
Mean (SD)	78.6 (16.8)	70.0 (19.3)	0.009**
Median (IQR)	81.9 (66.6–89.7)	71.2 (53.0–88.9)	
Platelet counts (per $mm^3 \times 104$)			
Mean (SD)	10.7 (3.5)	9.3 (4.9)	0.003**
Median (IQR)	10.2 (8.3–12.8)	8.2 (6.2–11.3)	
AFP			
Mean (SD)	36.5 (15.4)	32.3 (66.6)	0.007**
Median (IQR)	15.4 (6.1–40.3)	6.0 (0.0–28.0)	
Observation period (years)			
Mean (SD)	7.9 (3.7)	5.75 (3.9)	0.000**
Median (IQR)	7.0 (6.0–10.0)	5.0 (2.0–9.0)	

Abbreviations: BMI = body mass index; SD = standard deviation; IQR = interquartile range; M = male; F = female; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; AFP = α-fetoprotein; HCV-LC = hepatitis C virus-liver cirrhosis.
p-value, ANOVA; *$p=\chi^2$ test; **p, Kruskal Wallis test.

high proportion of male patients being among the excluded subjects was that the majority of the 25 habitual alcohol drinkers were male patients.

Platelet counts were more deteriorated in the excluded subjects. This seems also to be due to the existence of many habitual alcohol drinkers and patients who died within 3 years. The 132 included subjects were followed for >5 years. Of these, 41 were in the continuously high ALAT group, 48 in the continuously low ALAT group, and 43 in the unclassified (intermittently high) ALAT group. The average observation period in each group was 7.2±2.6 years in the continuously high ALAT group, 8.1±3.0 years in intermittently high ALAT group, and 8.6±3.4 years in continuously low ALAT group (Table II).

The characteristics of the patients in these three groups are presented in Table II. There were no significant differences in gender, smoking habit, serum albumin, prothrombin time, and platelet counts among these groups at the beginning of the study. However, there were significant differences in age and ASAT and ALAT levels. The average age in the continuously high ALAT group was slightly lower than that in the patients with continuously low ALAT levels. However it seems reasonable because the progress of the liver disease would be suspected to be earlier than in those with continuously low ALAT levels. Additionally, the ALAT level in patients excluded because of developing HCC within 3 years was 117.7±45.4 IU and was higher than that in the

Table II. Patient characteristics of continuously high, intermittently high and continuously low alanine aminotransferase groups on diagnosis of HCV-LC.

Characteristics	Continuously high ALAT group	Intermittently high ALAT group	Continuously low ALAT group	*p*-value
No. of cases	41	43	48	
No. of cases developed HCC	32 (78.0%)	26 (60.5%)	22(45.8%)	0.008
Age (years)				
Mean (SD)	57.7 (6.1)	58.2 (7.6)	61.3 (7.1)	0.034
Gender (M/F)	22/19	18/25	19/29	0.182*
Child classification (A/B)	41/0	43/0	48/0 1.000*	
BMI				
Mean (SD)	24.7 (2.7)	24.5 (2.9)	23.1 (3.2)	0.034
Smoking habit (+)/(−)	16/25	18/24	15/31	0.605*
Liver tests				
Albumin (g/dl)				
Mean (SD)	3.9 (0.4)	4.2 (1.2)	4.1 (1.5)	0.636**
Median (IQR)	3.8(3.5–4.2)	4.1(3.7–4.5)	3.9(3.7–4.2)	
ASAT (IU)				
Mean (SD)	107.3 (56.8)	110.9 (52.0)	64.4 (27.0)	0.000**
Median (IQR)	103.0 (75.5–133.0)	100.0 (79.5–136.3)	67.5(51.5–86.0)	
ALAT (IU)				
Mean (SD)	131.9 (65.9)	125.7 (72.3)	74.6 (48.7)	0.000**
Median (IQR)	123.0 (86.0–187.5)	109.0 (72.0–140.0)	68.0 (52.5–93.5)	
Prothrombin time (%)				
Mean (SD)	80.8 (13.3)	75.1 (13.7)	79.6 (17.1)	0.086*
Median (IQR)	83.3 (74.9–90.2)	78.7 (65.0–85.7)	82.6 (64.2–93.7)	
Platelet counts (per $mm^3 \times 10^4$)				
Mean (SD)	9.9 (3.1)	10.9 (4.1)	11.2 (3.2)	0.193**
Median (IQR)	9.6 (7.4–10.8)	10.0 (8.5–13.4)	10.7(8.6–13.5)	
AFP				
Mean (SD)	54.1 (76.7)	28.8 (45.0)	27.9 (39.9)	0.037**
Median (IQR)	24.1 (10.9–80.8)	13.1 (6.0–36.5)	13.0 (5.1–31.0)	
Observation period (years)				
Mean (SD)	7.2 (2.6)	8.1 (3.0)	8.6 (3.4)	0.165**
Median (IQR)	7.0 (5.0–8.5)	7.0 (6.0–10.0)	7.0 (6.0–11.0)	

Abbreviations: BMI = body mass index; SD = standard deviation; IQR = interquartile range; M = male; F = female; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; AFP = α-fetoprotein; HCV-LC = hepatitis C virus-liver cirrhosis.
p-value, unpaired *t*-test; *p, χ^2 test; **p, Mann-Whitney test.

132 patients included (108.9±64.1 IU) at the beginning of the study (p=0.249). The AFP level was slightly elevated in the continuously high ALAT groups. This seemed to be the result of continuous inflammation in this group of patients. The HCV-RNA level at the beginning of the study is not cited, because in many cases estimation of the HCV-RNA level was not undertaken at these days.

Figure 1 shows the cumulative incidence of HCC starting 3 years after the diagnosis of LC in patients with continuously high, continuously low, and unclassified (intermittently high) ALAT levels. The cumulative incidence of HCC in patients with continuously high serum ALAT levels for the first 3 years after the diagnosis of LC (Child Stage A) was significantly higher than that in patients with continuously low

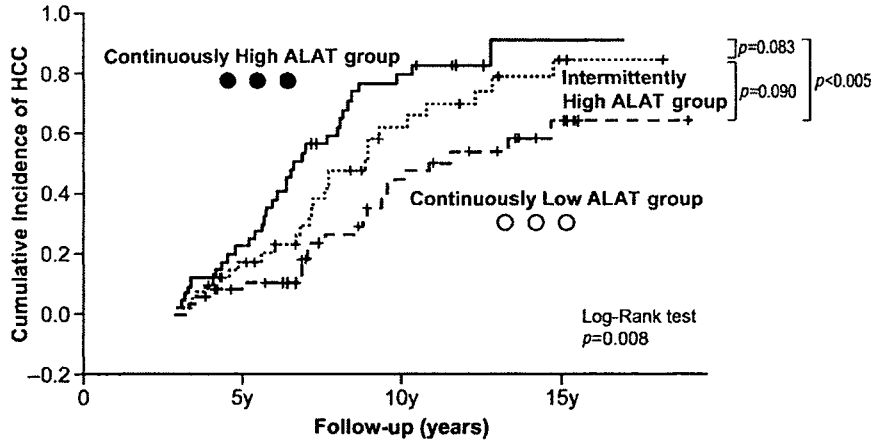

Figure 1. Cumulative incidence of hepatocellular carcinoma (HCC) starting 3 years after diagnosis of liver cirrhosis (LC) in patients with continuously high and continuously low serum alanine aminotransferase (ALAT) levels for the 3 years, and for those with intermittently high serum ALAT levels (Kaplan-Meier).

serum ALAT levels for the same period (p <0.005). The cumulative incidence of HCC in patients with intermittently high ALAT levels was higher than that in patients with continuously low serum ALAT levels, although the difference was not significant (p=0.090). There was also a tendency for the cumulative incidence of HCC in patients with continuously high ALAT levels to be higher than that in patients with intermittently high ALAT levels, but again the difference was not significant (p=0.083).

The 5-year incidence of HCC after classification of LC groups was 59% (11.8%/year) in the high ALAT group and 26% (5.2%/year) in the low ALAT group. The difference in cumulative incidence of HCC between the continuously high and continuously low groups was more marked in the period of less than 10 years after diagnosis of LC than in the period of more than 10 years after diagnosis; the ratio of incidence between these two groups at 8 years was 1.93-fold compared with 1.35-fold at 16 years after diagnosis (Figure 1).

In the univariate logistic analyses, as shown in Table III, the following four risk factors affected (p <0.20) the cumulative rate of incidence of HCC in all patients: gender, AFP, administration of SNMC, and ALAT group. As shown in Table III, the odds ratio of developing HCC in patients with continuously high serum ALAT levels was 5.1-fold that in patients with continuously low serum ALAT levels, while the odds ratio in patients with intermittently high ALAT levels was 1.5-fold that in patients with continuously low serum ALAT levels. Multivariate analysis using the logistic regression model showed that only one factor was statistically significant: the ALAT group (continuously high and continuously low ALAT group) independently contributed to HCC development (Table IV). Finally, if we assume the decrease in serum ALAT levels ≥25% to be an effective improvement, the effective improvement percentages in each drug are: SNMC (16 out of 31, 51.6%), UDCA (14 out of 36, 38.9%), Shosaiko-to (7 out of 24, 29.2%), a combination of SNMC and UDCA (18 out of 31, 58.1%).

Discussion

In this study we demonstrated that if high serum ALAT levels (≥80 IU) persisted for 3 successive years from the diagnosis of LC (Child Stage A), the 5-year incidence of HCC was markedly increased to as high as 59% (11.8%/year) in HCV-LC patients. It is clear that continuously high levels of ALAT in Child Stage A LC have a significant impact on the development of HCC. Thus, high ALAT levels (≥80 IU) for the 3 years following the diagnosis of LC can be highly predictive of the development of HCC. On this point, Mahmood et al. [28] also found that the 3-year annual average ALAT post-IFN therapy was significantly related to HCC occurrence in the HCV-associated chronic hepatitis patients with stage 3 fibrosis, although the tendency was more marked in our study with cirrhosis.

Many investigators have shown that patients with cirrhosis and high AFT levels have a high risk of developing HCC. Oka et al. [29] demonstrated that, in the cirrhotic patients without HBs-Ag, the cumulative incidence of HCC during a 5-year follow-up period was 28% in patients who had AFP levels of below 20 ng/ml at the time of entry, as compared with 44% in patients with AFP levels of 20 ng/ml or more.

In this study, we demonstrated that the continuously high serum ALAT levels for the first 3 years after diagnosis of LC was also as closely associated with the

Table III. Risk contributed to HCC development in univariate logistic model.

Items	*p*-value	Odds ratio	95% Confidence interval
Age	0.367	1.024	0.973–1.078
Gender (female)	0.167	0.592	0.282–1.246
BMI	0.997	1.000	0.879–1.138
Smoking habit	0.662	1.184	0.556–2.520
Albumin	0.356	0.862	0.629–1.182
Platelet counts	0.334	0.949	0.853–1.055
AFP	0.067	1.009	0.999–1.020
SNMC	0.101	1.864	0.886–3.922
UDCA	0.275	1.515	0.719–3.191
Sho-saiko-to	0.855	1.082	0.466–2.511
Juzen-taiho-to	0.913	0.921	0.210–4.047
Intermittently high ALAT	0.325	1.536	0.654–3.609
(reference: continuously low ALAT)			
Continuously high ALAT	0.002	5.120	1.816–14.433
(reference: continuously low ALAT)			

Abbreviations: HCC = hepatocellular carcinoma; BMI = body mass index; AFP = α-fetoprotein; SNMC = stronger-neo-minophagen C; UDCA = ursodeoxycholic acid; ALAT = alanine aminotransferase.

Table IV. Risk contributed to HCC development in a multivariate logistic model.

Items	*p*-value	Odds ratio	95% Confidence interval
Gender (female)	0.310	0.664	0.301–1.464
AFP	0.210	1.007	0.996–1.017
SNMC	0.501	1.327	0.581–3.029
Intermittently high ALAT	0.506	1.354	0.554–3.307
(reference: continuously low ALAT)			
Continuously high ALAT	0.013	3.931	1.336–11.565
(reference: continuously low ALAT)			

Abbreviations: HCC = hepatocellular carcinoma; AFP = α-fetoprotein; SNMC = stronger neo-minophagen C; ALAT = alanine aminotransferase.

development of HCC as the high AFP levels in the study by Oka et al. [29]. The odds ratio increased to 5.1-fold in patients with continuously high serum ALAT levels for the 3 years after diagnosis as compared with patients with continuously low ALAT levels for those years. In contrast, the odds ratio in patients with intermittently high ALAT levels was only 1.5-fold that of patients with low ALAT levels. Moreover, multivariate analysis confirmed that the ALAT group was independently associated with the development of HCC. Furthermore, the difference in cumulative incidence of HCC is more marked in the early period of follow-up than in the late period, suggesting the late occurrence of HCC in patients with continuously low ALAT levels for the 3 years following diagnosis of LC.

Recently many studies have demonstrated the close association between ALAT levels and the development of HCC. Ishiguro et al. [30] demonstrated that serum ALAT concentration was dependently associated with an increased risk of HCC in both virus-positive and virus-negative participants in a large population-based cohort study in Japan. Kurokawa et al. [31] studied the long-term effects of INF-alpha-2b plus ribavirin therapy on the incidence of HCC in patients with chronic hepatitis C and found that the cumulative incidence of HCC was significantly lower in patients who had average serum ALAT levels of <40 IU/L than in those who showed average serum ALAT levels of ≥40 IU/L after combination therapy. Moreover, Kumada et al. [32,33] surveyed the risk factors involved in the development of HCC in patients with chronic

HCV infection who had normal ALAT levels (<40 IU/L) over 10 years, and found that a slightly high ALAT level (>20 IU/L) was closely associated with the development of hepatocarcinogenesis.

The next issue is why the risk of developing HCC was increased so markedly in the continuously high ALAT group, as demonstrated in this study. It is likely that genetic alterations accumulate rapidly as inflammation persists and that the multistep process of carcinogenesis or promotion of tumor growth progresses more rapidly in patients with continuously high ALAT levels. In this respect, Ferenc et al. [34] demonstrated significant differences in the p53 expression between mildly, moderately, and severely inflamed biopsy samples in ulcerative colitis. 8-hydroxy-2′-deoxyguanosine (8-OHdG) is a pro-mutagenic DNA lesion produced by oxygen (hydroxy) radicals [35,36], and is known to be a parameter of genetic risk for hepatocarcinogenesis [37]. Furthermore, 8-OHdG was demonstrated to be involved in the initiation of rat liver hepatocarcinogenesis by low doses of N-nitrosodiethylamine (DEN) [38].

Shimoda et al. [39] examined the levels of 8-OHdG in patients with chronic hepatitis, liver cirrhosis, and HCC and found that the OHdG level in liver affected by chronic hepatitis was significantly higher than that in normal liver, and that the OHdG level in liver affected by cirrhosis also tended to be higher than that in normal liver. They also found a significant correlation between the OHdG content in non-cancerous liver tissue and individual serum ALAT levels, and concluded that chronic inflammation in the liver might produce oxidative DNA damage, which would increase the risk of genomic alterations causing hepatocarcinogenesis. If high-grade inflammation persists in the liver for many years, as in the continuously high ALAT group of patients in our study, the level of 8-OHdG might be high throughout the cirrhotic liver, resulting in the development of HCC.

Nowadays, patients with chronic hepatitis C in all countries are generally treated with IFN, and more than 50% of patients become HCV-RNA negative following PEG-IFN plus ribavirin therapy, but unfortunately, the IFN therapy is not effective in about 70% of patients with HCV-associated liver cirrhosis. Moreover, patients with HCV-associated cirrhosis carry a high risk of HCC, and in Japan, HCC actually develops in about 7% of those patients every year [40]. A strategy for preventing HCC development other than IFN therapy is therefore urgently needed for those patients.

In conclusion, we demonstrated that if the serum ALAT level was high (≥80 IU) for 3 successive years following the diagnosis of LC, then the risk of subsequently developing HCC increased markedly as compared with the continuously low ALAT group in Child A HCV-LC patients. Multivariate analysis confirmed that the ALAT group of LC was independently associated with HCC development. Thus, continuously high ALAT levels for 3 years following the diagnosis of LC (Child Stage A) can be highly predictive of the development of HCC. However, prospective trials using therapeutic approaches to decrease ALAT levels are necessary to confirm a positive impact of ALAT reduction on the incidence of HCC in patients with HCV-LC. The present study suggests that serum ALAT levels in HCV-LC patients must be lowered to below 80 IU by anti-inflammatory drugs as soon as a diagnosis of LC is confirmed.

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特集 緩和ケアチームの現状と展望

がん専門病院（がん診療連携拠点病院）緩和ケアチームの現状と地域連携

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Activity of Palliative Care Team at Oncology Center and Cooperation with Local Palliative Care Network: Esaki T*1, Takayama R*1, Higuchi Y*1 and Oshima A*1 (*1Palliative care team, National Kyushu Cancer Center)

The roles of palliative care team at oncology center are 1) Symptom control and psychosocial support of the cancer patient since the moment of initial diagnosis to the end of life combined with anti-cancer therapy, 2) Education for the medical staffs (oncologist, nurse, pharmacist, etc) about palliative care, 3) Cooperation with local network of palliative care institutions (hospice, clinic, nursing at home station) to offer palliative care to a patient and/or family without interruption. We are going to report the present activity of palliative care team at National Kyushu Cancer Center and a role in regional alliances of palliative care.

Key words: Oncology Center, Palliative care team, Education of palliative care for doctors, Cooperation with local palliative care network

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はじめに

近年，がん治療の初期段階からの緩和ケアの重要性が強調されるが，地域におけるがん医療の中心的役割を果たすがん診療連携拠点病院では，緩和ケアチームが中心となって緩和ケアを進めている．また，患者・家族の希望する療養場所を考えた場合，緩和ケアにおける地域連携は今後の大きな課題である．本稿では，がん専門病院としての九州がんセンター緩和ケアチームの現状と，緩和ケアの地域連携に果たす役割について述べる．

*1 国立病院機構九州がんセンター緩和ケアチーム

1 九州がんセンターの概要

九州がんセンターは総病床数411床のがん専門病院である．平成19年度の1日平均入院患者数は387.9人，平均在院日数22.4日，1日平均外来患者数355.5人である．2008年2月に都道府県がん診療連携拠点病院の指定を受けた．緩和ケア病棟は有していない．院内での死亡患者数は2003年度242人であったが，その後毎年減少し，2007年度は160人となっている．

2 がん診療連携拠点病院と緩和ケアチーム

福岡県のがん対策推進基本計画では，都道府県のがん診療連携拠点病院として九州がんセンターと九州大学病院が指定され，2病院による先駆的

表1　緩和ケアチームの役割

- 痛みやその他の身体症状の軽減と精神的，社会的，スピリチュアルな問題への支援
- 患者・家族とのコミュニケーション
- 倫理的側面からの助言
- 悲嘆のケア
- 医療従事者の支援
- 地域緩和ケアネットワークとの連携
- 教育活動と緩和ケアの普及
- 活動の定期的評価

文献2：日本緩和医療学会：緩和ケアチーム活動の手引きより

でより高度ながん医療の推進が求められている．その中で緩和ケアの推進は当院が中心となって担う役割のひとつである．また，厚生労働省の示すがん診療連携拠点病院の整備指針の中には，緩和ケアチームの整備，活動が盛り込まれている[1]．

緩和ケアチームの役割として日本緩和医療学会では**表1**のようなものを示している[2]．痛みをはじめとした身体的苦痛，精神的，社会的，スピリチュアルな苦痛などいわゆる全人的苦痛を軽減することとともに，地域緩和ケアネットワークとの連携，教育活動と緩和ケアの普及などもその役割とされている．

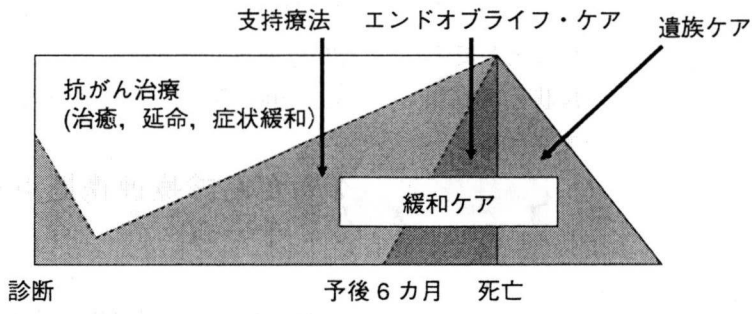
近年包括的がん医療という考え方が提唱され(**図1**)，がん医療において支持療法，エンドオブライフケア，遺族ケアは広義の緩和ケアとみなされるようになった[3]．がん専門病院においては，積極的な抗がん治療を行っていく時期の症状緩和および終末期のケアへの移行における役割が求められている．

終末期の療養の場の選択についてのアンケート調査では[4]，痛みを伴い予後が半年以下の末期状態とわかった場合，59%の人は自宅での療養を希望する．しかし，看取りの場については緩和ケア病棟を希望する人が50%，自宅が11%，病院が31%となる．がん専門病院での療養，看取りを希望する人はわずか3%にすぎない．病状の進行に伴って療養の場の希望は変化していくことがわかる．特に，末期状態において自宅で過ごしたいと考える多くの患者・家族に，いつでも，どこでも，切れ目のない緩和ケアを提供していく体制(医療機関の連携)を整備していく必要がある．

3 九州がんセンター緩和ケアチームの概要

九州がんセンターでは1993年より心療内科によるコンサルテーション型のリエゾン活動が始まった．これが2003年にサイコオンコロジー科へ移行し，緩和ケアチームの設立準備を開始した．緩和ケアチーム設立委員会を設置して，チームメンバーや活動内容について検討し，2004年4月1日よりコンサルテーション型・緩和ケアチーム活動を開始した．チーム回診，カンファレンス，教育活動，疼痛アセスメントシートや緩和ケアマニュアルの作成などさまざまなシステムの整備を行った．その後，2006年11月より，緩和ケアチーム専従医師，専従看護師を配置し，緩和ケア診療加算の算定を開始した．

当院緩和ケアチームの構成は，専従医師1名(サイコオンコロジー科)，専任医師3名(身体



文献3：Education in Palliative and End-of-life Care for Oncology 2007より改変

図1　包括的がん医療(Comprehensive Cancer Therapy)

症状緩和担当2名，精神症状緩和担当1名），専従看護師1名（がん看護専門看護師），専任看護師3名（がん性疼痛看護認定看護師2名，ホスピス病棟経験看護師1名），薬剤師1名，臨床心理士1名，医療ソーシャルワーカー（MSW）1名の計11名である．患者・家族および担当医，担当看護師を，専従医師，専従看護師を中心とした多職種のスタッフでサポートする体制である．構成員の問題点として身体症状緩和担当医師が専従となっていないこと，麻酔科の参加がないことがあげられる．

チーム活動の柱は，1）コンサルテーション型の緩和ケアチームとしてチームメンバーによる診療と緩和ケアの提供（随時）．2）週1回のチームカンファレンスおよびメンバー全員での全病棟の回診．3）教育の一環として，全職員対象，医師向け，看護師対象の勉強会の定期的な開催である．

緩和ケア診療加算の算定を開始してからの活動実績は，毎月の新規依頼件数が平均30件，緩和ケア診療加算算定件数が約400件となっている．緩和ケアチーム依頼時の主訴は，不安，抑うつ，せん妄といった精神症状が全体の6割を占め，残りが痛みを中心とした身体症状となる．これは，当院の緩和ケアチームがサイコオンコロジー科を母体としていることと関連している．

緩和ケアチームへの依頼は，担当医だけでなく，病棟の担当看護師からも可能である．看護師はアセスメントシートを用いて疼痛を評価し，コントロールが不十分と判断すれば担当医と相談の上チームの介入を依頼する．チームのメンバーは担当医，看護師とともに疼痛マネジメントについて検討し，緩和ケア実施計画書を作成し，患者本人に渡す．

緩和ケアチームではスタッフ教育の一環として全職種対象の緩和ケア勉強会を年に6回定期的に開催している．これには他施設の医師，看護師も多数参加している．2008年度の勉強会のテーマは，神経障害性疼痛の診断と治療，精神症状緩和ケア，医療用麻薬と服薬指導，呼吸困難の緩和ケア，緩和ケアにおけるコミュニケーション・スキル，デスカンファレンスであった．

4 がん診療に携わる医師に対する緩和ケア研修会

厚生労働省は，がん対策推進基本計画において「すべてのがん診療に携わる医師が研修等により，緩和ケアについての基本的な知識を習得する」ことを目的として掲げた[5]．これを受けて2008年4月，各都道府県に対して厚生労働省健康局長通知「がん診療に携わる医師に対する緩和ケア研修会の開催指針」が出された[6]．また，がん診療連携拠点病院の整備に関する指針[1]によると，当該2次医療圏において，がん医療に携わる医師を対象とした緩和ケアに関する研修会を毎年定期的に開催することが求められている．開催指針においてはその内容について準拠すべき「緩和ケア研修会標準プログラム」が示されている．日本緩和医療学会ではPEACEプロジェクト（Palliative care Emphasis on symptom management and Assessment for Continuous medical Educationの略）として，この開催指針に準拠したプログラムの緩和ケア研修会を実施するために必要な教材からファシリテーターマニュアルまでを「パッケージ」として提供し，また，教育方法などのノウハウを提供する指導者研修会を開催している[7]．

福岡県では，15の都道府県および地域がん診療連携拠点病院が分担して，県内数千人に上ると見られるがん診療に携わる医師を対象とした，緩和ケア研修会を開催していく予定である．当院でも，指導者研修会での研修内容を踏まえ，2009年夏から開催する予定で，緩和ケアチームが中心となって準備を進めているところである．

5 緩和ケアチーム活動への満足度評価

当院緩和ケアチームでは2008年1月，緩和ケアチーム活動に対する医療者の満足度やニーズを明らかにすることを目的として，当院の医師，看護師，薬剤師，MSW，栄養士など計338名の職員に対してアンケート調査を行った．その中で，緩和ケアチーム活動体制の満足度に関しては，情

報や方針の共有，コミュニケーション・相談のし易さ，依頼システムなど60～80%の職員がおおむね満足であると回答した．また緩和ケアチームに依頼したい内容については，痛みを含めた身体症状，精神症状の評価とマネジメントに加えて，緩和ケア移行支援や外来緩和ケアなどの希望が少なからず見られ，特に緩和ケア外来に関しての具体的な内容からは，入院からの診療の継続および緩和ケアに関する地域連携についてのニーズが多いことが伺われた．

6 緩和ケア外来

当院では2008年4月より緩和ケア外来を開設した．これはがん診療連携拠点病院の整備指針にも盛り込まれているが，外来通院患者および他施設（一般病院，在宅療養支援診療所など）からの紹介患者を対象として，「痛みの緩和ケア外来」および「こころの緩和ケア外来」として，それぞれ週1回診療日を設けている．当院には緩和ケア科や緩和ケア病棟がなく，純粋に緩和ケアのみを目的とした患者ではなく，主に外来で抗がん剤治療などを継続中の患者で痛みのコントロールが不十分な患者が対象となる．しかし，身体症状緩和担当医は他の専門領域との兼任医であり，外来患者へのタイムリーな対応ができないことも多く，当院の課題となっている．

7 退院調整連携

当院では四国がんセンターの退院調整連携パス[8]をモデルとして，入院患者のスムーズな退院をめざした退院連携調整プログラムの試みを開始している．入院後早期に，医師・病棟看護師が，退院に向けた支援の必要性をスクリーニングし，必要性があると判断した場合には，早期に相談支援・情報センターの退院調整看護師やMSWが介入していく．この院内連携の強化が地域への連携につながるものと考え，取り組みを開始したところである．進行がん患者の場合，この地域連携は緩和ケアの連携となることが多く，緩和ケアチームのメンバーでもある退院調整看護師，MSWは，緩和ケアチームと連携して支援の必要性を検討している．

8 「緩和ケア依頼書」と「緩和ケア事前情報書（第一報）」を用いた医療連携

緩和ケア目的で緩和ケア施設（ホスピス，在宅療養支援診療所）や一般病院に患者の紹介や打診を行う際に，最低限必要な事項を共通のシートで共有し，患者・家族へ切れ目のない医療を提供することを目的として，「緩和ケア依頼書（依頼書）」および「緩和ケア事前情報書（事前情報書）」を用いた緩和ケアの地域連携に取り組んでいる．これは，当院および近隣のホスピス，在宅クリニックなど数施設の医師，MSWが中心となり作成し，2007年6月より当院から緩和ケア目的での患者紹介を行う際に利用している．

依頼書（**図2**）は，主治医が記載して診療情報提供書に添付してFAX・郵送する書類であり，紹介の目的，経緯，告知の状況，予後などについてほとんどの項目をチェックボックス形式で記入する．事前情報書は，MSWが本人・家族との面談，看護師から得た情報を記載してFAX，郵送する．保険などの基本情報，家族構成，理解している告知の状況，ADLの基本状況などを記載する．これらの書類は，限られた調整時間の中で，紹介元，紹介先双方の多忙な医師，看護師，MSWが，受け入れの判断材料となる情報を確実に伝えることに主眼を置いて運用されている（九州がんセンターホームページ[9]よりダウンロード可能）．

当院では2007年6月から2008年5月までの1年間で，292名の患者を対象として，県内外の61施設に対して375件の依頼書，事前情報書の利用を行った．当時直接患者を診療する医師67名中57名が依頼書を利用していた．2008年6月に行った依頼書，事前情報書を利用した担当者の意識アンケートによると，紹介先の担当者からは，連携が容易になった，ケアの継続に活用できたなどの回答がえられ，当院の医師からも，情報の共有化に有効であった，記入の負担は最小限で

20　年　月　日

緩和ケア依頼書

病院名　：＿＿＿＿＿＿＿＿＿＿＿＿　＿＿＿＿＿＿＿＿＿＿＿＿先生

患者氏名：＿＿＿＿＿＿＿＿（　　歳）□：男　□：女　□：入院中（　　病棟）　□：外来

1．　**依頼目的**

□：入院予約　□：外来通院での症状コントロール　□：在宅療養（往診含む）

- **紹介元への通院の有無**

□：なし　□：あり　頻度（　　に　　回程度）

- **（在宅療養中）紹介元で緊急時の受入れについて**

□：可能　□：不可　□：相談後検討　□：その他（　　）

2．　**患者さんに最初に緩和ケアを勧めた人について**

□：患者さん本人が自分で希望

□：家族などからの勧め（□配偶者、□子供、□親戚、□両親、□友人、□その他（　　））

□：医療関係者（□医師、□看護師、□薬剤師、□その他の医療者）

3．　**緩和ケアを紹介した経緯について**（複数選択可　最も強い理由には丸をつける）

□：治療の効果が期待できなくなったため

□：本人が希望するため　□：家族が希望するため

□：症状コントロールのため　□：終末期の看取りのため

□：その他　（　　）

4．　**現時点での病気病状について、どこまで説明や告知をしたか**

a）患者さん本人に対して

時期：20　年　月頃　（化学療法中□、後□、放射線療法中□、後□、手術後□）

□：癌であることを告知していない　□：病名のみ（癌であることのみ）

□：転移再発部位や広がりを含めて　□：余命を含めて

b）家族に対して

時期：20　年　月頃　（化学療法中□、後□、放射線療法中□、後□、手術後□）

誰に対して行ったか（□配偶者、□子供、□親戚、□両親、□友人、□その他（　　））

□：癌であることを告知していない　□：病名のみ（癌であることのみ）

□：転移再発部位や広がりを含めて　□：余命を含めて

5．　**上記の病状説明を患者本人と家族とどちらを先にしたか**

□：患者自身が先　□：家族が先　□：患者と家族に同時に

6．　**患者さんの臨床的な予後はどれくらいあると考えるか**（複数選択可）

□：6ヶ月以上　□：3ヶ月以上　□：2ヶ月程度　□：1ヶ月程度　□：2週間程度

□：1週間ほど　□：1週間以内　□：急変あり（出血、呼吸苦、消化管穿孔、　　）

備考

病院名　：＿＿＿＿＿＿＿＿＿＿＿＿　医師名　：＿＿＿＿＿＿＿＿

2008.7.22改定

図2　緩和ケア依頼書

すむ，予後や病状の告知，抗がん治療や緩和ケアの目的などインフォームドコンセントを行う際の内容や意識に変化があったなどの回答が得られた．

ちなみに，MSWへホスピス転院の依頼があってから転院が完了するまでの期間は，2007年度平均11.9日であったが，2008年上半期9.8日と短縮が見られている．

現在，この依頼書，事前情報書は，当院からの紹介患者だけではなく，2次医療圏，県内の他の医療機関からの緩和ケア目的の紹介の際にも利用が広まっている．

9. 緩和ケアネットワーク

地域における緩和ケアのネットワークを考える上で，地域にどのような緩和ケアのリソースがあるのかを知ることは重要である．福岡県内には20施設の緩和ケア病棟を有する病院があり，総病床数は約350床を数え，全国の緩和ケア病棟入院料届出病床数の約1割をしめる（2008年4月日本ホスピス緩和ケア協会）[10]．この数は全国でも突出しており恵まれた環境といえる．都道府県および地域がん診療連携拠点病院15施設にそれぞれ緩和ケアチームがある．また，在宅療養支援診療所約600施設，訪問看護ステーション約230箇所，居宅介護支援事業所約1300施設があるが，このうちどれだけの施設がどの程度在宅緩和ケアに取り組んでいるかは把握できていない．

最近，福岡地区12のホスピス緩和ケア病棟を持つ施設が中心となり，ホスピス緩和ケアネットワーク福岡が設立された．設立趣旨は，ホスピス緩和ケアに関係する，ホスピス緩和ケア病棟，ホスピス緩和ケアクリニック，訪問看護ステーション，介護施設などがネットワークを構築し，がん患者および家族の療養環境を整え，シームレスなケアを提供することとなっており，最大の目的は在宅緩和ケア医の育成である．また，福岡県は，県内13の保健所に地域在宅医療支援センターを作り，患者家族の相談・支援，在宅緩和ケアの普及を図る目的の在宅医療推進事業を進めている．がん診療連携拠点病院で行う医師を対象とした緩和ケア研修会は，地域，二次医療圏の医師が対象となり医師同士の顔が直接見えるため，ネットワーク作りには最適と考えられる．

緩和ケアのネットワークにおいて，一つのネットワークですべてを網羅することは不可能と考えられる．複数のネットワークがさらに相互に連携しあうことが重要と考えられる．がん専門病院の緩和ケアチームには，そのネットワークの一つの核としての活動が求められる．

まとめ

九州がんセンター緩和ケアチームのがん専門病院（がん診療連携拠点病院）としての役割は，まず第一に，緩和ケア外来を含めた，抗がん治療と平行した症状緩和，終末期がん患者の症状緩和といった緩和ケアの提供である．次に，専門病院として院内，院外医療従事者への緩和ケア教育を行うことである．特に，がん対策推進基本計画に基づいた，がん診療に従事する医師に対する緩和ケア研修会の開催は非常に重要なものとなる．最後に，緩和ケアの地域連携は，がん専門施設から緩和ケア施設へのシームレスな（切れ目のない）連携として，相談支援・地域医療連携室とともに，緩和ケアチームが中心となって進めるべき重要な役割である．

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Phase I Study of the Sequential Administration of S-1 and Cisplatin for Metastatic Gastric Cancer

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Abstract. *The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) has been reported to be active against metastatic gastric cancer (MGC) and great synergy has been shown in vivo and in vitro when 5-FU precedes CDDP. The sequential combination of S-1 (tegafur, oxonic acid, 5-chloro-2,4-dihydroxypyridine) followed by CDDP for MGC was investigated. A phase I trial applying increasing doses of oral administration of S-1 (65-80 mg/m^2) for 21 days and increasing doses of CDDP (60-80 mg/m^2) on day 22 every 35 days was conducted in order to determine the maximum tolerated dose (MTD) and recommended phase II dose. Patients with metastatic or recurrent gastric cancer, no prior chemotherapy, measurable disease, ECOG performance status less than 3 and adequate organ functions were eligible for the study. Three patients were treated at each dose level with escalation based on toxicity. Fifteen patients were included and evaluated for dose-limiting toxicity (DLT) and MTD. DLT included NCICTC grade 3 anorexia and fatigue in patients treated at S-1 80 mg/m^2 and CDDP 80 mg/m^2 (dose level 5). The other toxicities, grade 3 or higher, included neutropenia (grade 3) and nausea/vomiting (grade 3). Non-hematological toxicities were grade 1/2 and included diarrhea, nausea and stomatitis. There was no treatment-related mortality. Therefore, the recommended dose was a combination of S-1 at 80 mg/m^2 and CDDP at 70 mg/m^2. This sequential administration of S-1 and CDDP every 35 days is tolerable and warrants a phase II trial. A multicenter phase II study is currently under way.*

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Key Words: S-1, CDDP, metastatic gastric cancer, phase I study, combination chemotherapy.

Although the survival benefit of 5-fluorouracil (5-FU)-based chemotherapy has been shown, in comparison to the best supportive care (BSC) for unresectable advanced or metastatic gastric cancer (MGC) patients (1-3), the prognosis of such patients is still poor, with a median survival of less than 9 months. In order to improve the clinical efficacy of chemotherapy for patients with MGC, many clinical trials employing anticancer agents such as 5-FU, cisplatin and new classes of drugs, such as taxanes and irinotecan, have been conducted. However, no specific regimen has shown survival benefit superior to that of continuous infusion of single agent 5-FU in randomized phase III clinical trials (4). Therefore, it is still necessary to develop effective chemotherapy for MGC.

S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-FU, 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits dihydropyrimidine dehydrogenase, and potassium oxonate (Oxo), which is protective against tegafur-inducing toxicity (5). The feasibility of single agent S-1 for MGC was assessed in phase I and early phase II studies and a recommended regimen of 80 mg/m^2/day, oral administration for 28 consecutive days, followed by a 14-day interval was established. The clinical activity of S-1 for MGC is reported to be 26% to 45% (6-8). Combination therapy of S-1 was also attempted with other agents such as CDDP, irinotecan and taxanes (9-12). The S-1 plus CDDP regimen was one of the most promising combination therapies and a phase I/II trial revealed a prominent response rate of 76% and mean survival time (MST) of 12.6 months (9). This study was scheduled as S-1 at 40 mg/m^2 twice daily for 21

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Table I. *Summary of the toxicities experienced in all cycles.*

Dose level (n)	1 (3 patients)				2 (3 patients)				3 (3 patients)				4 (3 patients)				5 (3 patients)			
Dose of S-1	65 mg/m^2				65 mg/m^2				80 mg/m^2				80 mg/m^2				80 mg/m^2			
Dose of CDDP	60 mg/m^2				70 mg/m^2				60 mg/m^2				70 mg/m^2				80 mg/m^2			
NCI-CTC Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Toxicity (n)																				
Leukocyte	1	0	0	0	1	1	0	0	0	2	0	0	2	0	0	0	0	1	0	0
Neutrocyte	0	1	0	0	1	1	0	0	0	2	0	0	2	0	0	0	0	0	1	0
Platelet	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemoglobin	0	1	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0	1	0	0
ALT	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Nausea/Vomiting	2	0	0	0	2	0	1	0	1	2	0	0	0	1	1	0	1	0	2	0
Fatigue	0	2	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0
Anorexia	2	0	0	0	0	2	0	0	1	1	0	0	0	2	0	0	0	1	2	0
Alopecia	2	0	ϕ	ϕ	1	0	ϕ	ϕ	0	0	ϕ	ϕ	0	0	ϕ	ϕ	0	0	ϕ	ϕ
Fever	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

n: Number of patients

consecutive days and a 2-h infusion of CDDP at 60-70 mg/m^2 on day 8, followed by a 14-day interval.

The combination of 5-FU and CDDP has been shown to exhibit great synergy in *in vitro* and *in vivo* studies when 5-FU precedes CDDP (13, 14). Since this sequence-dependent interaction would be exhibited in a combination of S-1 and CDDP, a phase I trial was conducted applying increasing doses of S-1 (65-80 mg/m^2) for 21 days and increasing doses of CDDP (60-80 mg/m^2) on day 22 every 35 days. This report presents the safety data of this regimen and recommends doses of the agents for phase II trial.

Patients and Methods

Patients. The main eligibility criteria included a histologically proven, unresectable, locally advanced or metastatic gastric adenocarcinoma; age, 20 to less than 75 years; Eastern Cooperative Oncology Group (ECOG) performance status, 2 or less; measurable disease; leukocyte count 3,500/mm^3, or more; neutrophil count 1,500/mm^3, or more; platelet count 100,000/mm^3, or more; serum creatinine 1.5 mg/dl, or less; serum bilirubin 2.0 mg/dl, or less; aspartate aminotransferase (AST) 100 IU/l or less; alanine aminotransferase (ALT) 100 IU/l, or less; a life expectancy of 3 months or more; and no prior chemotherapy or radiotherapy except adjuvant chemotherapy more than 30 days prior to entry. This study was approved by the local Ethics Committee at each institution and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study.

Patients with the following criteria were not eligible: central nervous system metastasis with neurological symptoms, unresolved bowel obstruction or diarrhea, and known contraindication to fluorouracil (angina pectoris, myocardial infarction in the past 6 months).

Study design and treatment. The study was designed as a phase I dose-finding study to determine the maximum tolerated dose (MTD) and recommended dose of S-1 and CDDP. Treatment consisted of CDDP in 500 ml of saline, given intravenously (*i.v.*) over a 120-min period with appropriate hydration. The MTD was defined as the dose level associated with the same dose-limiting toxicity (DLT) in at least two out of three, or two out of six patients. DLT was defined as the occurrence of one or more of the following National Cancer Institute (NCI) common toxicity criteria (CTC): grade 3 or greater nonhematological toxicity, except for nausea and vomiting; grade 4 neutropenia lasting for more than 4 days; grade 3 neutropenic fever; or grade 4 thrombocytopenia.

Drug administration and dose escalation. S-1 was administered orally for 21 consecutive days and CDDP was administered on day 22, and cycles were repeated every 35 days. The starting dose of S-1 was 65 mg/m^2 plus CDDP 60 mg/m^2. Dose escalation then proceeded as listed in Table I. No intrapatient dose escalation was permitted during the study. The number of patients per dose level was based on any DLT experienced during cycles 1 and 2. If a DLT was observed in one of the first three patients treated at a particular dose level, three further patients were recruited. If the same DLT occurred in two out of the six patients, this dose was defined as the MTD.

Treatment was continued until evidence of progression, unacceptable toxicity, or patient refusal. S-1 administration was delayed if, on the planned day of treatment, there was leukopenia (leukocytes less than 3,000/mm^3); platelets less than 75,000/mm^3; total bilirubin, ALT and AST more than three times the upper limit of the normal range; serum creatinine more than 1.2x the upper limit of the normal range; or nonhematological toxicities greater than grade 3, except for nausea and vomiting. When the S-1 treatment was delayed over 21 consecutive days, the administration was restarted after the disappearance of the above causes and was continued over 21 days. If a delay exceeded more than 8 days, the present course was discontinued and starting of the next course was postponed until recovery. When a next course was not started 15

days after the planned day, treatment was discontinued. CDDP administration was delayed on day 22, if leukocytes were less than 2,000/mm^3; platelets less than 50,000/mm^3; serum creatinine more than 1.2x the upper limit of the normal range; creatinine clearance less than 50 ml/min; or diarrhea greater than grade 2. When these causes still remained on day 31, CDDP treatment was skipped and the next cycle was started after a 14-day interval. When a patient experienced DLT, S-1 was reduced by approximately 20% and CDDP was reduced by 10 mg/m^2. In the event of life-threatening toxicities, treatment was definitively interrupted. To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists and/or dexamethasone were administered *i.v.* before chemotherapy. Granulocyte colony-stimulating factor (G-CSF) was used when neutrophils were reduced to 500/mm^3 or there was febrile neutropenia (neutrophils less than 1,000/mm^3).

Assessability, toxicity and response criteria. The pretreatment evaluation included a history and a physical examination, performance status assessment, complete blood count with differential and platelet counts, complete blood profile, carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, urinalysis, ECG, chest radiograph or computed tomography (CT) scan, abdominal CT scan and/or ultrasonography, and any other appropriate diagnostic procedure to evaluate the metastatic sites. During treatment, a physical examination was performed every week, a complete blood cell count twice a week and a blood profile and urinalysis every week. Sites of metastatic disease were re-evaluated every 8 weeks. Chest radiography and/or an abdominal CT scan or ultrasonography were repeated at least every 3 months, if there was no evidence of lung or abdominal disease. Toxicities were monitored weekly and were scored according to standard NCI-CTC. Responses were evaluated every 8 weeks according to the World Health Organization criteria.

Results

Patient characteristics. Fifteen patients were enrolled in this study. There were 9 men and 6 women. The median age was 61 years, with range of 44 to 72 years. ECOG performance status was 0 to 1 in the 15 patients. Ten patients were unresectable and 5 patients had a recurrent tumor. No patient had prior chemotherapy, including adjuvant setting chemotherapy. Four patients out of 15 had only the original gastric lesion, 7 patients had the original gastric and metastatic lesion, and 4 patients had a metastatic lesion alone. The average number of chemotherapy cycles was 3.6, with range of 1 to 17 cycles.

Dose escalation. The first three patients received S-1 at 65 mg/m^2 and CDDP at 60 mg/m^2 (dose level 1) and, because after two cycles no DLT had occurred, the subsequent group of three patients received S-1 at 65 mg/m^2 and CDDP at 70 mg/m^2 (dose level 2; Table I). After confirming that no DLT had occurred in the patients at each dose level, dose escalation proceeded to level 3 (S-1 at 80 mg/m^2 and CDDP at 60 mg/m^2) and subsequently level 4 (S-1 at 80 mg/m^2 and CDDP at 70 mg/m^2). Since DLT did not occur in these 6 patients at dose levels 3 and 4, an additional three patients were recruited at dose level 5 (S-1 at 80 mg/m^2 and CDDP at 80 mg/m^2). Two out of three patients at this dose level had grade 3 anorexia and grade 3 fatigue. As a result, two out of three patients had DLT at level 5 and this level was considered as the MTD. Therefore, the recommended phase II dose is S-1 80 mg/m^2 and CDDP 70 mg/m^2.

Toxicity. All patients were assessable for toxicities. There was no treatment-related death in the entire number of cycles in the study. A summary of the hematological toxicity is listed in Table I. At dose level 5, only one of the three patients experienced grade 3 neutropenia. All other hematological toxicities in all cycles were less than grade 2. Overall, no patient required dose reduction of S-1 and CDDP. Three out of 51 cycles were delayed for more than 7 days because of toxicity. G-CSF was not used for neutropenia in this study. As a result, the relative dose intensities for S-1 and/or CDDP, calculated as the actual dose delivered divided by the intended dose, were 93.1% and 87.2% respectively at all courses and 100% and 100% at dose level 4. A decrease of platelets below 75,000/mm^3 (grade 2 or greater) was not observed in any of the cycles. The effects on red blood cells were also mild. Anemia below 8.0 g/dl (grade 3 or greater) did not occur. Nonhematological toxicities were major problems in this study. The incidences of major nonhematological toxicities are listed in Table I. Two patients with grade 3 anorexia and one patient with grade 3 fatigue were observed in the first cycle of dose level 5. These symptoms completely disappeared several days after stopping the administration. Grade 3 nausea was observed in two patients at dose level 5, one at dose level 4 and one at dose level 2.

Response. Response to therapy was a secondary outcome and was measured in all patients. All patients were assessable for response. Of the 15 patients, 3 experienced a partial response (PR) and 5 had stable disease (SD) (Table II). An overall response rate of 20.0% was observed. Two patients out of 10 patients with the original gastric lesion showed a PR (20.0%). However, one out of 6 patients with liver metastasis and none of 3 patients with peritoneal lymph nodes metastasis had PR.

Discussion

S-1 is currently the one of the most promising agents against MGC in Japan. According to several clinical trials of combination chemotherapy using S-1 and CDDP, the combination therapy shows a superior response rate and feasibility. Koizumi *et al.* reported a response rate of 76% for Japanese MGC patients in a phase II study (9) and a 49% response rate was observed in Western MGC patients (15), although the administration schedule and doses of these agents were different.

Table II. *Patient characteristics.*

Level	Gender	DLT	Response	No. chemotherapy cycles	Reasons for discontinuation	Survival (days)
1						
1-1	F	-	NC	3	Patient's withdrawal	866.0
1-2	M	-	NC	4	PD	638.0
1-3	M	-	NC	4	PD	544.0
2						
2-1	M	-	PR	4	Gastrectomy	1537.0
2-2	F	-	NC	4	PD	638.0
2-3	F	-	PR	17	Unknown	1448.0
3						
3-1	M	-	PD	3	PD	361.0
3-2	M	-	PD	1	PD	156.0
3-3	M	-	PR	2	Doctor's decision	584.0
4						
4-1	M	-	NC	2	PD	175.0
4-2	F	-	PD	2	PD	404.0
4-3	M	-	NE	2	Unknown	414.0
5						
5-1	F	-	NE	1	Doctor's decision	198.0
5-2	M	G3 Fatigue G3 Anorexia	NE	1	Adverse events	606.0
5-3	F	G3 Anorexia	NE	1	Adverse events	146.0

NC, No change; RR, partial response; PD, progressive disease; NE, not evaluable; DLT, dose-limiting toxicity.

The present study employed sequential administration of S-1 and CDDP based on the rationale obtained by preclinical studies showing that 5-FU preceeding CDDP augmented the cytotoxicity of CDDP or could even circumvent CDDP resistance by inhibiting the repair machinery of CDDP-induced platinum-DNA interstrand crosslinks (13). The excision repair enzyme, ERCC1, has been shown to be involved in the repair of CDDP-induced DNA damage (16); 5-FU-mediated down-regulation of the expression of its gene may account for this synergy (17). In addition, reduction of glutathione contents due to 5-FU-induced inhibition of gamma-glutamylcysteine synthetase (gamma-GSC) was also been shown as a mechanism for the synergistic effect (18).

In the phase I trial of single administration of S-1, leukocytopenia and gastrointestinal toxicities more than grade 3 were reported to appear in the patients with rates of 7-10% (6, 7). A dose-escalation study was designed, starting with a reduced amount of S-1 in levels 1 and 2 and a standard dose of S-1 was administered in levels 3-5 for combination with CDDP. The safety profile of the present protocol demonstrated that hematological toxicities more than grade 3 were not shown in all courses at levels 1-4 but grade 3 neutropenia appeared at level 5 (1 out of 15 cases). In addition, nonhematological toxicities more than grade 3, namely anorexia (2 out of 15 cases) and fatigue (1 out of 15 cases), were observed. Therefore level 4 was considered to be the recommended phase II dose.

As previously reported, the recommended doses of 80 mg/m^2/day of S-1 may result in considerable toxicities in the patients in Western countries (6, 19, 20). Ajani *et al.* reported a phase II trial of 50 mg/m^2/day (day 1-21) of S-1 and 75 mg/m^2 (day1) of CDDP for MGC to show 26% of patients with fatigue and 13% with anorexia, which were both more than grade 3 (15). A phase II study with administration of S-1 for 21 days and 60 mg/m^2 (day 8) of CDDP for Japanese MGC patients showed incidences of severe neutropenia (16%), anemia (16%), anorexia (26%), nausea (16%) and diarrhea (5%; (9)). The other phase I/II study in Japan with S-1 for 14 days and 70 mg/m^2 CDDP (day 8) resulted in 9.1% of patients with severe neutropenia (21). Therefore, the present study with higher S-1 and CDDP dose intensities showed equivalent or less toxicity than the previous reports. It may be possible that S-1 administered prior to CDDP could achieve a higher dose intensity more safely. Several randomized phase III studies for MGC employing cytotoxic and molecular targeting drugs are ongoing and their results may strongly reflect establishing a standard therapy for MGC (22-27).

Conclusion

Sequential S-1 plus CDDP administration in this study was feasible and might be a promising therapy for MGC. A phase II study using the recommended doses is currently underway.

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The adenocarcinoma-specific stage shift in the Anti-lung Cancer Association project: Significance of repeated screening for lung cancer for more than 5 years with low-dose helical computed tomography in a high-risk cohort☆

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ABSTRACT

Background: We investigated whether a stage shift occurs during long-term repeated screening for lung cancer with low-dose helical computed tomography (LDCT) in a high-risk cohort.
Methods: A total of 2120 subjects (mean age, 63 years; 87% male and 83% smokers) were continuously recruited and underwent repeated screening with LDCT from 1993 through 2004.
Results: Nineteen lung cancers were detected at baseline examinations (prevalence cancers), and 57 lung cancers were detected at subsequent examinations (incidence cancers). For both prevalence cancers and incidence cancers, adenocarcinoma (74% and 63%, respectively), especially invasive adenocarcinoma (42% and 23%, respectively), was the most common histological diagnosis, and stage IA was the most common pathological stage (58% and 79%, respectively). The detection rate of incidence cancers other than bronchioloalveolar carcinoma became significantly higher after 5 years of LDCT examinations ($r = 0.50$, $P = 0.020$). Moreover, both the percentage of cancers of stage II–IV and tumor size became significantly lower for invasive adenocarcinoma after 5 years of LDCT examinations ($r = -0.77$, $P = 0.007$ and $r = -0.60$, $P = 0.029$, respectively).
Conclusions: Repeated screening for more than 5 years might demonstrate the efficacy of LDCT screening for lung cancer through an adenocarcinoma-specific stage shift.

1. Introduction

Lung cancer is considered as an appropriate disease for screening because it is the leading cause of cancer death worldwide, symptomatic disease is generally lethal, localized disease can be managed curatively, and high-risk cohorts can be defined on the basis of tobacco consumption [1]. However, screening with chest X-ray films or sputum cytological examination has failed to reduce lung-cancer mortality rates in randomized, controlled trials [2–6].

Low-dose helical computed tomography (LDCT) is a promising screening method because a higher percentage of asymptomatic, X-ray–invisible, or stage IA lung cancers (mostly adenocarcinoma) are found with baseline or repeated computed tomography (CT) examinations than with conventional screening methods [7–11]. In fact, according to the results of the International Early Lung Cancer Action Program, the 10-year survival rate for all patients with lung cancer was 80% regardless of stage or treatment [12]. If the cancer was in clinical stage I and was promptly resected, the 10-year survival rate was 92%. However, because large, randomized, controlled trials of LDCT screening are still in progress [13,14], whether LDCT screening reduces lung-cancer mortality rates remains uncertain. Although mortality data are needed to determine whether LDCT screening is effective, indirect evidence for a possible mor-

Abbreviations: CT, computed tomography; LDCT, low-dose helical computed tomography; BAC, bronchioloalveolar cell carcinoma; ALCA, Anti-lung Cancer Association.

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