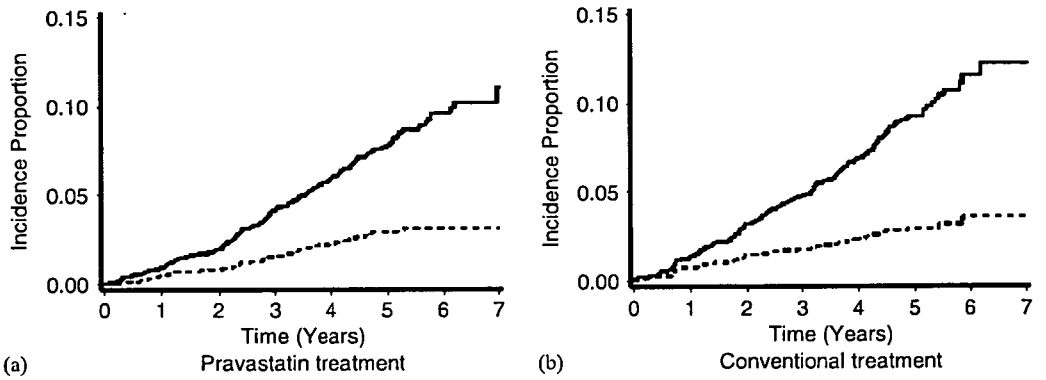

Figure 1. Peterson bounds for the marginal incidence proportion of CHD events in each treatment group. The solid line is one extreme scenario, in which subjects with competing events were assumed to experience CHD immediately after censoring. The dashed line is the other extreme scenario, in which subjects with competing events were assumed to be censored at the end of all follow-up.

Table II. The distributions of event times (years) of CHD and competing events.

Treatment group		Types of events			
		CHD	Loss to follow-up	Death due to causes other than CHD	All competing events*
Pravastatin	Number	65	53	68	121
	Mean	2.76	4.52	3.14	3.74
	Median	2.83	4.65	2.91	3.89
	Quartiles	1.67,3.74	3.99,5.57	2.09,4.15	2.34,5.03
	Range	0.19,5.30	0.16,7.46	0.22,7.25	0.16,7.46
Conventional	Number	48	44	63	107
	Mean	2.42	4.33	3.27	3.70
	Median	2.12	4.66	3.23	4.05
	Quartiles	1.00,3.73	4.08,4.97	2.15,4.33	2.55,4.71
	Range	0.05,5.86	0.31,6.65	0.71,7.29	0.31,7.29

*All competing events are 'loss to follow-up' plus 'death due to causes other than CHD'.

times are infinite. We regarded such competing events as censored at the end of all follow-up (the end of 1997). The usual treatment group-specific Kaplan–Meier estimates that ignore the competing risks, that is, the incidence proportion curves that censor all competing events at their event times, were almost the same as the lower bounds in each group. These observations were due to the fact that in each group most CHD events were likely to occur before the competing events, as shown in Table II. In this paper, we want to estimate the marginal incidence proportion in each treatment group, which will lie in between these two extreme scenarios.

3. IPCW METHODS

3.1. Assumption of no unmeasured confounders for censoring

Let T_i and C_i be the potential failure (occurrence of CHD events) time and the potential censoring time for subject i ($i = 1, 2, \ldots, n$), respectively. C_i

is the minimum of C_{ij} $(j = 1,2,3)$, where C_{i1} denotes a death time due to causes other than CHD, C_{i2} denotes a censoring time of loss to follow-up, and C_{i3} denotes a censoring time at the end of follow-up. Censoring at the end of follow-up was not considered dependent censoring, because there was a fixed known calendar date at which the follow-up of all subjects ended (31/12/1997 for the KLIS data); therefore, C_{i3} was known for all subjects. The observable data are n i.i.d. copies of $X = \min(T, C_1, C_2, C_3)$, type of event J ($J = 0$, if CHD events are observed), treatment group indicator variable R ($R = 1$ if pravastatin treatment group, and $R = 0$ if conventional treatment group), and covariate history $\overline{\mathbf{V}}_X$, where $\overline{\mathbf{V}}_t = \{\mathbf{V}_s : 0 \leqslant s \leqslant t\}$, and $\mathbf{V}_s$ is a vector of possibly time-dependent prognostic factors for T recorded at time s.

In order to identify the marginal survival, we assume the following relation in the censoring process:

$$\lambda_{C_j}(t|R, \overline{\mathbf{V}}_t, T, T > t) = \lambda_{C_j}(t|R, \overline{\mathbf{V}}_t, T > t) \qquad (1)$$

where $j = 1,2$ and $\lambda_{C_j}(t \mid (\cdot), T > t)$ is the cause-specific hazard of censoring at time t given both $X = \min(T, C_1, C_2, C_3)$ exceeds at t and the information in $(\cdot)$. This assumption means that, conditional on the treatment group and on the recorded history until time t, the cause-specific hazard of censoring C_j at time t does not depend on the possibly unobserved CHD event time T. We also assume an additional conditional independence assumption that the competing events C_j are independent of each other given the treatment group and the covariate history. This fundamental assumption is called 'no unmeasured confounders for censoring' [16] and is equivalent to a sequential version of Rosenbaum and Rubin's strong ignorability assumption [17]. The assumption specifies that, among subjects with the same recorded past, the population of subjects censored due to each specific cause at time t has the same distribution of the outcome of interest as that of the population of uncensored subjects at time t. The assumption will be satisfied, in particular, when the censoring process is ignorable or MAR (missing at random) in the terminology of missing data analysis. In practice, we would not expect this assumption to be precisely true, but given a rich collection of prognostic factors recorded in $\overline{\mathbf{V}}_t$, it may well be approximately true.

3.2. IPCW marginal survival time

The IPCW approach is to regard subjects with competing events as dependently censored the first time a subject either died or was censored by loss to follow-up. To correct for dependent censoring, we need to estimate the treatment group-specific hazards of censoring conditional on time-dependent prognostic factors for CHD [14]. The time-dependent Cox proportional hazards model for censoring is used for the right-hand side of equation (1),

$$\lambda_{C_j}(t|R, \overline{\mathbf{V}}_t, T > t) = \lambda_{0RC_j}(t) \exp(\alpha_{RC_j} \overline{\mathbf{V}}_t) \qquad (2)$$

where for each reason of censoring j $(j = 1,2)$, the treatment group-specific baseline hazard $\lambda_{0RC_j}(t)$ and the treatment group-specific regression parameters α_{RC_j} are assumed, because both the baseline hazard and covariate effects may depend on treatment group. For estimating the hazard of a particular censoring type conditional on covariates, CHD events and other censoring types are censored at their event times.

Under the assumption of no unmeasured confounders for censoring (1) and the proportional hazards model for cause-specific hazards of censoring (2), the conditional probability of being uncensored for subject i is provided by the following time-dependent extension of the Kaplan–Meier estimator for censoring j,

$$\hat{K}_{ij}(t) = \prod_{u; X_u < t, \sigma_{uj} = 1, R_u = R_i} \exp[-\hat{\lambda}_{0RC_j}(X_u) \exp(\hat{\alpha}_{RC_j} \overline{\mathbf{V}}_{iX_u})]$$

where $\hat{\lambda}_{0RC_j}(X_u) = \sigma_{uj} / \sum_{i=1}^{n} \exp(\hat{\alpha}_{RC_j} \overline{\mathbf{V}}_{iX_u}) Y_i(X_u) I(R_i = R)$ is the Breslow estimator of the baseline hazard function for censoring j in treatment group R, and $Y_i(t)$ takes the value of one if subject i is at risk at time t, and zero otherwise. σ_{uj} takes the value of one if the subject is censored for reason j, and zero otherwise. For any proposition A, $I(A)$ equals one if A is true and zero otherwise.

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The IPCW estimator is different from the ordinary estimator by weighting the contribution of a subject at risk by the inverse of the conditional probability of having remained uncensored. Using the above estimator of uncensored probability, the contribution of a subject at risk at time t is weighted by the inverse of an estimate of the conditional probability of having remained uncensored for both reasons until time t, $\hat{W}_i \times (t) = (1/\hat{K}_{i1}(t)) \times (1/\hat{K}_{i2}(t))$. Here, we assume that the conditional probabilities are bounded away from zero with probability 1 for each subject i, that is, $\hat{K}_{ij}(t) > 0$. This assumption will be satisfied unless their conditional probabilities are structural zero, that is, $\hat{K}_{ij}(t) = 0$ for some values of $\overline{\mathbf{V}}_i$. Under this assumption, the IPCW Kaplan–Meier estimator of the treatment group-specific marginal survival of not having CHD events through time t is

$$\hat{S}_T(t|R) = \prod_{\{i:X_i<t\}} \left\{ 1 - \frac{\delta_i \hat{W}_i(X_i) I(R_i = R)}{\sum_{u=1}^{n} Y_u(X_i) \hat{W}_u(X_i) I(R_u = R)} \right\} \tag{3}$$

where δ_i is the failure time indicator that takes the value of one if the subject failed and zero if the subject is censored. This IPCW Kaplan–Meier estimator for CHD events in treatment group R differs from the ordinary Kaplan–Meier estimator in that the contribution of a subject at any time X_i is weighted by the subject-specific weight $\hat{W}_i(X_i)$. In the IPCW estimator (3), the quantity, $\delta_i \hat{W}_i(X_i) I(R_i = R)$, estimates the number of subjects in treatment group R who would have been observed to fail at time X_i in the absence of any competing event, while the quantity, $\sum_{u=1}^{n} Y_u(X_i) \hat{W}_u(X_i) I(R_u = R)$, estimates the number of subjects who would have been alive and at risk at time X_i in the absence of any competing risk. Thus, the ratio estimates the hazard of CHD event at X_i in the absence of competing event; it follows that (3) estimates the probability $S_T(t|R)$ of surviving without failure (i.e. of remaining CHD-free) until time t in the absence of competing event. When (1) and (2) are true, Robins [12] proves that under mild regularity conditions, the IPCW estimator (3) gives a consistent estimator of our target causal estimand $S_T(t|R)$, that is, the marginal survival function. Inverse probability weighted estimators have been previously considered by Horvitz and Thompson [18] in the sample survey literature. Satten and Datta [19] give an elementary discussion of the IPCW estimators.

If the IPCW estimate (3) is close to the Peterson lower bound, we will see that the competing events are related to the unobserved CHD events and that these dependent competing risks can be explained by the covariates $\overline{\mathbf{V}}_i$ included in the analysis based on (2). On the other hand, if the IPCW estimate (3) is close to the Peterson upper bound, we will see that the competing events are not dependent ones under the assumption (1) that all important covariates were included in the covariate history based on (2). Therefore, it is important to compare the IPCW estimate (3) with the bounds in order to evaluate the degree and the direction of the selection bias.

3.3. Comparison of the IPCW marginal survival time

We used the Cox proportional hazards model to compare the marginal distribution between the two treatment groups. The model is

$$\lambda_T(t|R) = \lambda_0(t) \exp(\beta R) \tag{4}$$

where $\lambda_T(t|R)$ is the hazard of CHD events at time t in treatment group R. The IPCW Cox partial likelihood score $U(\beta)$ for β differs from the ordinary Cox partial likelihood score in that the contribution of the subject u at risk at time X_i is weighted by $\hat{W}_u(X_i)$, that is,

$$U(\beta) = \sum_{i=1}^{n} \delta_i \hat{W}_i(X_i) \times \left\{ R_i - \frac{\sum_{u=1}^{n} Y_u(X_i) \hat{W}_u(X_i) R_u \exp(\beta R_u)}{\sum_{u=1}^{n} Y_u(X_i) \hat{W}_u(X_i) \exp(\beta R_u)} \right\} \tag{5}$$

If (1) and (2) are correct, Robins [12] proves that under mild regularity conditions, the weighted estimating equations $U(\beta) = 0$ gives a consistent and asymptotically normal estimator of the parameter β.

The use of individual weights induces within-subject correlation and we must take this correlation into consideration in the calculation of variance. In the calculation of a confidence interval, we used the robust variance estimate [20,21]. It provides a conservative confidence interval for the parameter of interest, that is, the 95% Wald confidence interval calculated as $\beta \pm 1.96\times$ (robust standard error), which is guaranteed to cover the true value of β at least 95% of the time in large samples [21,22]. We programmed the above procedure to obtain the IPCW estimate using SAS/IML procedure.

3.4. Adjustment of confounding by the IPTW method

In comparative studies, where investigators do not control treatment assignment, the directly estimated treatment effect can be strongly affected by confounding. This implies that in the KLIS data we cannot directly use the weighted log-rank-test (5) to compare the IPCW marginal incidence between treatment groups. There has been an enormous amount of work devoted to analytic adjustments for confounding. A new class of causal models called marginal structural models (MSMs) has recently been proposed [22,23] to estimate the causal effect of treatment from observational data. In MSMs, the parameters are consistently estimated by the Inverse Probability of Treatment Weighted (IPTW) method. Here, we briefly describe the rationale for the method in the special case of a binary point treatment such as the KLIS data. A formal mathematical definition of MSMs using the counterfactual outcomes has been provided by Robins [23].

We consider the association model (4). In this subsection, we assume that there is no censoring, so the failure time T is observed on each subject. If a treatment assignment is completely at random and noncompliance is absent, the probability of receiving a treatment will be independent of both measured and unmeasured baseline prognostic factors, that is, there is no confounding. In this case, assuming that the association model (4) is correct, β has a causal interpretation, because association implies causation in the absence of confounding. This situation is called that a treatment is 'causally exogenous' [22,23]. On the other hand, if the probability of receiving a treatment is independent of only measured baseline prognostic factors, a treatment is said to be 'statistically exogenous' [22,23]. It must be noted that the fact that a treatment is statistically exogenous does not imply that it is causally exogenous, because unmeasured confounders may predict the probability of receiving a treatment. We can empirically test whether a treatment is statistically exogenous, but not whether it is causally exogenous.

Suppose that we can correctly model the probability of receiving a treatment as a function of measured baseline prognostic factors $\mathbf{V}_0$. We could then quantify the degree to which the treatment is not statistically exogenous by the quantity,

$$W_{IPTW} = \frac{\Pr(R)}{\Pr(R \mid \mathbf{V}_0)}$$

where the denominator is the probability that a subject received his or her own observed treatment given measured prognostic factors $\mathbf{V}_0$, while the numerator is the unconditional probability that a subject received his or her own observed treatment. The numerator and denominator of W_{IPTW} are equal, if the treatment is statistically exogenous.

When the treatment is not statistically exogenous, we consider estimating β in the association model (4) by a weighted Cox regression in which a subject is given the weight W_{IPTW}. Weighting creates a pseudo-population where each subject is copied W_{IPTW} times. In this pseudo-population, the treatment is statistically exogenous and thus causally exogenous under the assumption of no unmeasured confounders. The weighted Cox regression estimator is called an IPTW estimator [22,23]. As given in the Appendix 1 of Robins *et al.* [22], in a simple stratified point treatment analysis, the IPTW estimator is identical to the standardized estimator with the total group as the standard population. Hence, the MSM is interpretable as a nonparametric multivariate standar-

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dization method [24]. The weighted Cox regression to obtain the IPTW estimate can be performed with SAS/PHREG procedure using the 'WEIGHT' statement.

4. ANALYSIS OF KLIS DATA

To estimate the subject-specific weight $\hat{W}_i(X_i)$, we used five time-dependent factors as well as 12 baseline factors in the time-dependent Cox proportional hazards model for censoring (2). Prognostic factors at baseline were age (categorized as – 49 (reference category), 50–54, 55–59, 60–64, 65–69, and 70–74, with dummy variables for this categorization), serum HDL cholesterol (categorized as $-<40$ (reference category), $40-<48$, $48-<57$, and 57−mg/dl), serum LDL cholesterol (mg/dl), total cholesterol (categorized as $-<235$ (reference category), $235-<246$, $246-<262$, and 262−mg/dl), triglycerides (mg/dl), body mass index (BMI, categorized as $-<22.0$ (reference category), $22.0-<24.0$, $24.0-<25.9$, and $25.9-\text{kg/m}^2$), current smoking (dichotomous), diabetes mellitus (dichotomous), daily alcohol use (dichotomous), prior use of lipid-lowering drugs (dichotomous), hypertension (dichotomous), and angina pectoris (dichotomous). Time-dependent prognostic factors were serum HDL cholesterol, serum LDL cholesterol, total cholesterol, triglycerides, and the occurrence of cerebral infarction measured at six, 12, 24, 36, 48 and 60 months after a subject entered this trial. For these five time-dependent factors, the most recent recorded values were included as covariates in the prediction model (2) for the conditional probabilities of having remained uncensored. All these variables are clinically important prognostic factors for CHD events. The variable-selection procedures to reduce these variables to a relevant subset were not used, because it is important to include as many prognostic factors both for CHD events and for censoring as possible for the validity of our analysis, that is, the assumption (1) of 'no unmeasured confounders for censoring '.

Figure 2 shows the IPCW marginal incidence proportion of CHD events in each treatment group. In each group, the upper solid line is the Peterson bound, in which subjects with competing events were assumed to experience CHD immediately after censoring. In both treatment groups, the marginal incidence for CHD was almost the same as the lower bound in which subjects with competing events were assumed to be censored at the end of all follow-up. Therefore, there is little evidence of dependent competing risks in the KLIS data.

Because the KLIS was an observational study, we adjusted the baseline confounding by the IPTW method described in Section 3.4. We modeled the probability that a subject received the pravastatin

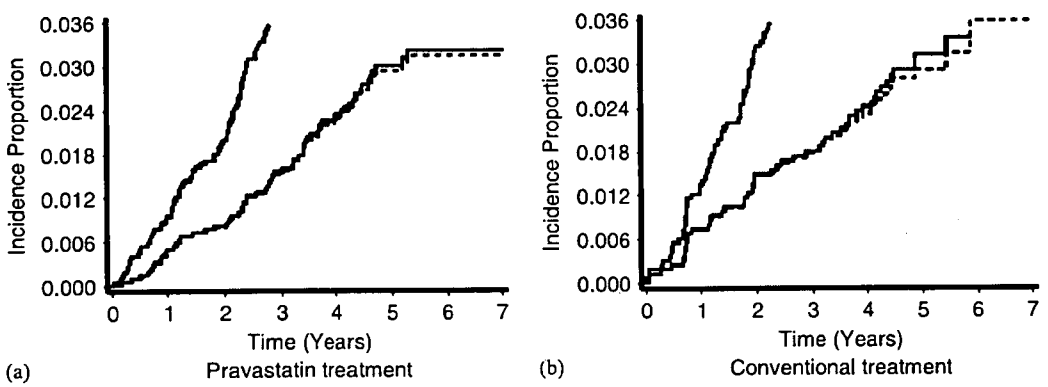

Figure 2. The IPCW marginal incidence proportion of CHD events in each treatment group. In each group, the upper solid line is the Peterson upper bound and the dashed line is the lower bound.

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treatment using logistic regression with the 12 baseline factors described above as explanatory variables. From this logistic regression model, estimates of the subject-specific weight, $\hat{W}_i^*$, the inverse of the conditional probability of receiving his or her own observed treatment, were obtained. The subject-specific weight $\hat{W}_i(X_i) \times \hat{W}_i^*$ was used instead of $\hat{W}_i(X_i)$ or $\hat{W}_u(X_i)$ in the weighted score function (5). This weight is the inverse of the probability that a subject would have his or her own observed treatment and uncensored history for both reasons through time t. Figure 3 shows the results. A marginal treatment effect (hazard ratio = 0.78; 95% Wald confidence interval: 0.51–1.18) was observed after adjustments for baseline confounding as well as competing risks.

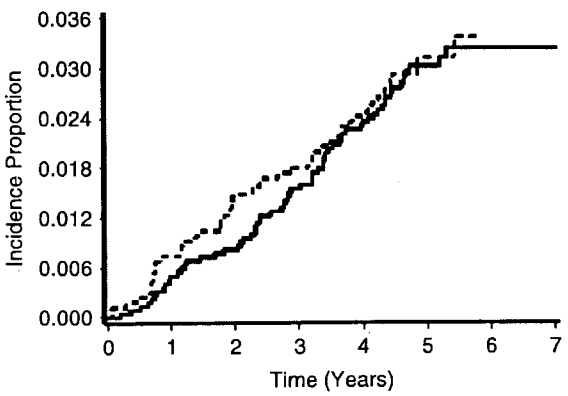

Figure 3. Comparison of the IPCW marginal incidence proportion of CHD events between treatment groups. Baseline confounding was adjusted by the IPTW method. The solid line is the pravastatin treatment group and the dashed line is the conventional treatment group.

Table III shows a comparison of hazard ratio and the 95% confidence interval under five adjustment methods. First analysis compared treatment effect without taking account of both baseline confounding and competing risks, in which competing events were assumed to be censored at their event times (hazard ratio = 0.97 ; 95% CI: 0.67–1.41). Second analysis compared treatment effect with an adjustment by the IPCW method taking account of only competing risks using the weighted log-rank-test (5) (hazard ratio = 0.94; 95% CI: 0.65–1.37). Third analysis compared treatment effect with an adjustment by the IPTW method taking account of only baseline confounding using the estimates of the subject-specific weight, $\hat{W}_i^*$, in which competing events were assumed to be censored at their event times (hazard ratio = 0.80; 95% CI: 0.53–1.20). Fourth analysis compared treatment effect with an adjustment by both the IPCW and the IPTW method, that is, Figure 3 (hazard ratio = 0.78; 95% CI: 0.51–1.18). A slightly stronger evidence of baseline confounding was observed with the crude result biased toward the null. However, the confidence intervals of the hazard ratio using different adjustment methods overlapped with each other. This might be due to the fact that the distributions of competing events were similar between treatment groups (Table II) and the KLIS was originally started as a randomized clinical trial [1, 2].

Final analysis compared treatment effect with an adjustment by the Cox regression models including all baseline covariates as the linear predictors and assuming all competing events to be censored at their event times (hazard ratio = 0.85; 95% CI: 0.57–1.27). It must be noted that,

Table III. Comparison of treatment effect.

No.	Analysis method	Hazard ratio	95% confidence interval
1*	No adjustments	0.97	0.67–1.41
2	Adjustment by the IPCW method	0.94	0.65–1.37
3*	Adjustment by the IPTW method	0.80	0.53–1.20
4	Adjustments by both the IPCW and IPTW methods	0.78	0.51–1.18
5*	Adjustment by the Cox regression model	0.85	0.57–1.27

*Competing events were assumed to be censored at their event times. In analysis No. 5, all baseline confounders were included as the linear predictors in the Cox regression model.

aside from the competing risks problems, this final result depends heavily on the correct specification of the parametric model forms, which are usually unknown in most epidemiologic applications, while our IPTW adjustments of confounding do not need such parametric assumptions.

5. DISCUSSION

The problem of analyzing and interpreting data concerning competing risks continues to be one of the most important and vexing in biostatistical practice. The analyses of competing risks can be made using observable population parameters. An important observable quantity is the cumulative incidence functions based on the cause-specific hazards [25–28]. Alternatively, in this paper, we presented a method for estimation and comparison of treatment group-specific marginal survival curves of time to event data in the presence of dependent competing risks. The parameter of interest in our analysis is the marginal survival distribution, which is the net probability of time to event if only one cause of event acted on a population [4, 29, 30]. The ability to isolate the effect of one risk acting a population is attractive, especially if the focus of a study is to evaluate the effect of an intervention that is targeted at reducing incidence from that specific cause. Much of the literature on competing risks approaches such a problem by assuming the existence of latent survival times for each subject, that is, the estimation of event rates for certain types of event given the removal of some or all other event types. However, the net probabilities are hypothetical quantities and not directly observable in a population. Only observable quantities are their bounds, which allow for any possible dependence structure and will often be too wide to be of value [9–11]. Therefore, it is necessary to assume some model concerning the censoring process such as (1) to identify the net probabilities from the available information on the observables including covariate histories.

The proposed method is a straightforward extension of Robins and Finkelstein [14] for settings with two or more reasons for censoring. The application of the proposed methodology to the KLIS data suggested that the IPCW marginal incidence for CHD was almost the same as the lower bound. We included as many covariates as possible to predict the conditional probabilities of having remained uncensored. This result may suggest that there was little evidence of dependent competing risks in the KLIS data. In many studies, because we cannot safely say that the dependent censorings have not occurred, it is important to conduct the analysis accounting for the dependent censorings as well as the standard one and to compare their results. When their results differ remarkably, the reasons for drop-outs are examined in detail and the effects on the final conclusion in the study should be discussed. On the other hand, when the results are nearly the same ones like the KLIS data, dependent censorings observed in the study does not cause a severe selection bias attributable to the covariates and the results from the standard analysis are robust in relation to the censorings.

It must be noted that the low incidences for the competing events do not always mean that the IPCW estimate will be close to the lower bound. The issue of interest in our analysis is whether the competing events are informative for their unobserved CHD events and whether the relation can be explained by the observed covariate histories. If they have much information on their unobserved CHD events and the covariates are available to explain the dependency, the IPCW estimate will be close to the upper bound without regard to the incidence of competing events. On the other hand, if they have little information on their unobserved CHD events, the IPCW estimate will be close to the lower bound.

For example, in a cohort of 100 subjects, suppose that at the time of 2 (years) from the start of follow-up, 5 subjects and 3 subjects experienced CHD events and non-CHD deaths, respectively, and that the remaining 92 subjects were censored at the end of study (time = 5). In this hypothetical data, the upper and lower bound

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of the incidence rate is $8/(5 \times 2 + 3 \times 2 + 92 \times 5) = 1/59.5$ and $5/(5 \times 2 + 3 \times 5 + 92 \times 5) = 1/97$, respectively. Under the independent censoring, the incidence rate is $5/(5 \times 2 + 3 \times 2 + 92 \times 5) = 1/95.2$. If a binary covariate V is available and the distribution is $V = 1$ for both 5 CHD and 3 non-CHD events and $V = 0$ for 92 censored events at time = 5, the IPCW weights are 8/5 for the former events and 1 for the latter events. In this scenario of dependent competing risks, the IPCW incidence rate is $5 \times 1.6/(5 \times 2 \times 1.6 + 3 \times 2 \times 1.6 + 92 \times 5 \times 1) = 1/60.7$, which is almost the same as the upper bound. On the other hand, if the distribution of V is $V = 1$ for 5 CHD events and $V = 0$ for the other events, the IPCW weights are 1 for the former events, and are 95/92 (time $\leqslant 2$) and 1 ($2 <$ time $\leqslant 5$) for the latter events. In this scenario of independent competing risks, the IPCW incidence rate is $5 \times 1/(5 \times 2 \times 1 + 95 \times 2 \times 95/92 + 92 \times 3 \times 1) = 1/96.4$, which is almost the same as the lower bound. For more formal explanations, see Scharfstein and Robins [15] and Scharfstein *et al.* [31], in which the relation between the IPCW estimator and the bounds is discussed. They showed that, as the censoring bias parameters α in (2) goes to $\pm\infty$ (although they consider the case where the cause-specific hazard of censoring depends also on the possibly unobserved event time T given $\overline{V}_t$), the resulting IPCW estimator will converge to the bounds.

Our results are based on a nonidentifiable assumption concerning the residual dependence between time to events and competing risks due to unmeasured factors. The ordinary Kaplan–Meier estimator does not utilize recorded information on time-dependent covariates $\overline{V}_t$ and assumes the independence among competing risks, while the IPCW one utilizes such information and assumes the conditional independence among them. However, because causal interpretation of IPCW estimates depends on the correctness of assumption (1), making the censoring process ignorable is more important than fitting a parsimonious model in (2). As Joffe *et al.* [32] have described in the modeling of competing causes of death, the aggregation of censoring by competing causes may obscure important differences in the effect of various predictors on each type of censoring and so lead to misspecification of the model for censoring. Therefore, we fitted separate models for each type of censoring, where the treatment group-specific baseline hazard and regression parameters were assumed for each competing risk. Furthermore, in the KLIS, many clinically important time-dependent factors were measured and all of them were used as covariates to predict the probability of remaining in the study. Therefore, there will be a certain degree of validity in our IPCW estimates.

Otherwise, it will be necessary to develop sensitivity analysis methodology to investigate the sensitivity of our inferences to the fundamental assumption (1) of no unmeasured confounders. This sensitivity analysis will be particularly important for our data, in which the IPCW marginal incidence was almost the same as the lower bound. A simple and easy sensitivity analysis is to generate a hypothetical prognostic factor both for CHD and for competing events and to include the factor in the prediction of the conditional probabilities of uncensored. In the KLIS data, a hypothetical binary time-dependent covariate with a hazard ratio of 40.0 for both CHD and competing events was randomly generated and was included in the estimation of the subject-specific weight in addition to the 17 covariates described in Section 4. The increase of the resulting IPCW incidence in each group was slight compared with the estimates (Figure 2) ignoring the effect of the hypothetical unmeasured covariates. Therefore, in the KLIS data, it is likely that the effect of unmeasured confounders on our inferences would be small. Scharfstein *et al.* [15, 31] have developed more formal sensitivity analysis. The sensitivity analysis for our data using their idea will be future work.

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ORIGINAL ARTICLE

A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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Abstract
Purpose The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
Patients and methods Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
Results Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
Conclusion Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

Keywords Irinotecan · Phase II study · Pancreatic cancer · Chemotherapy · Pharmacokinetics

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Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

Patients and methods

Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) ≥ 50 points; estimated life expectancy ≥ 2 months; adequate bone marrow function (WBC count $< 12{,}000$ per mm^3, neutrophil count $\geq 2{,}000$ per mm^3, platelet count $\geq 100{,}000$ per mm^3, and hemoglobin level ≥ 10.0 g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institutional upper limit of normal), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, serum transaminases levels ≤ 2.5 times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per mm^3, thrombocytopenia of $< 100{,}000$ per mm^3, fever (≥ 38°C) with suspected infection, grade ≥ 1 or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of < 500 per mm^3, thrombocytopenia of $< 50{,}000$ per mm^3, fever (≥ 38°C) with suspected infection, or grade ≥ 2 or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/m^2. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a < 50% reduction or a < 25% increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a $\geq$ 25% increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of $\geq$ 50% from baseline for $\geq$ 4 weeks, or a decreased morphine consumption of $\geq$ 50% from baseline for $\geq$ 4 weeks. A positive response for KPS was defined as an improved KPS of $\geq$ 20 points from baseline for $\geq$ 4 weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for $\geq$ 4 weeks.

Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at −20°C until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

Results

Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of ≥ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

Table 1 Patient characteristics ($n = 37$)

Characteristics		No. of patients (%)
Gender		
Male		25 (67.6)
Female		12 (32.4)
Median age, years (range)	59 (41–74)	
Karnofsky performance status, point		
100		8 (21.6)
90		25 (67.6)
80		4 (10.8)
Median body surface area (m^2) (range)	1.55 (1.31–1.85)	
History of surgical resection		7 (18.9)
PTBD		2 (5.4)
Sites of metastasis		
Liver		33 (89.2)
Lymph nodes		17 (45.9)
Lung		8 (21.6)
Others		3 (8.1)

PTBD percutaneous transhepatic biliary drainage

Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).

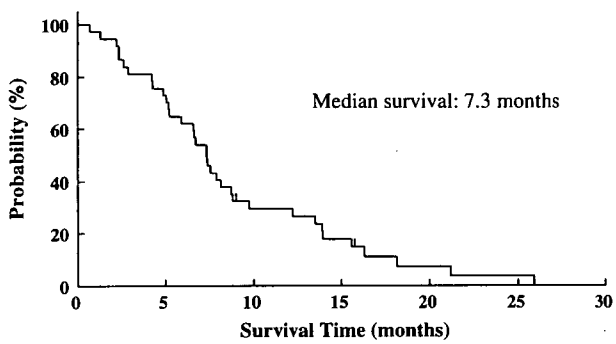

Fig. 1 Overall survival curve of all 37 patients

Table 2 Efficacy results

	No. ($N = 37$)	%
Tumor response		
Partial response	10	27.0
No change	7	18.9
Progressive disease	17	45.9
Not evaluable	3	8.1
Time to progression (months)		
Median	2.1	
Range	0.7–9.5	
Overall survival (months)		
Median	7.3	
Range	0.7–25.9	
1-year survival rate		29.5

Table 3 Clinical benefit response ($n = 14$)

		Karnofsky performance status		
		Improved	Stable	Worse
Pain	Improved	0	2	0
	Stable	0	6	1
	Worse	0	5	0

Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

Table 4 Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4 (%)	Grade 3–4 (%)
	1	2	3	4		
Hematologic						
Leukopenia	15	6	8	1	81.1	24.3
Neutropenia	5	11	8	2	70.3	27.0
Anemia	0	14	3	0	45.9	8.1
Thrombocytopenia	1	1	1	1	10.8	5.4
Non-hematologic						
Nausea	7	12	15	–	91.9	40.5
Vomiting	7	14	5	0	70.3	13.5
Diarrhea	15	8	4	0	73.0	10.8
Constipation	1	8	2	0	29.7	5.4
Anorexia	4	7	14	1	70.3	40.5
Stomatitis	2	0	0	0	5.4	0
Rash	1	0	0	0	2.7	0
Alopecia	24	1	–	–	67.6	–
Fatigue	3	8	1	1	35.1	5.4
Fever	3	1	0	0	10.8	0
Infection	2	1	4	1	21.6	13.5
Total bilirubin	4	1	1	0	16.2	2.7
AST	5	5	2	0	32.4	5.4
ALT	4	4	3	0	29.7	8.1
Hyponatremia	6	0	3	0	24.3	8.1
Creatinine	0	0	2	0	5.4	5.4

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these

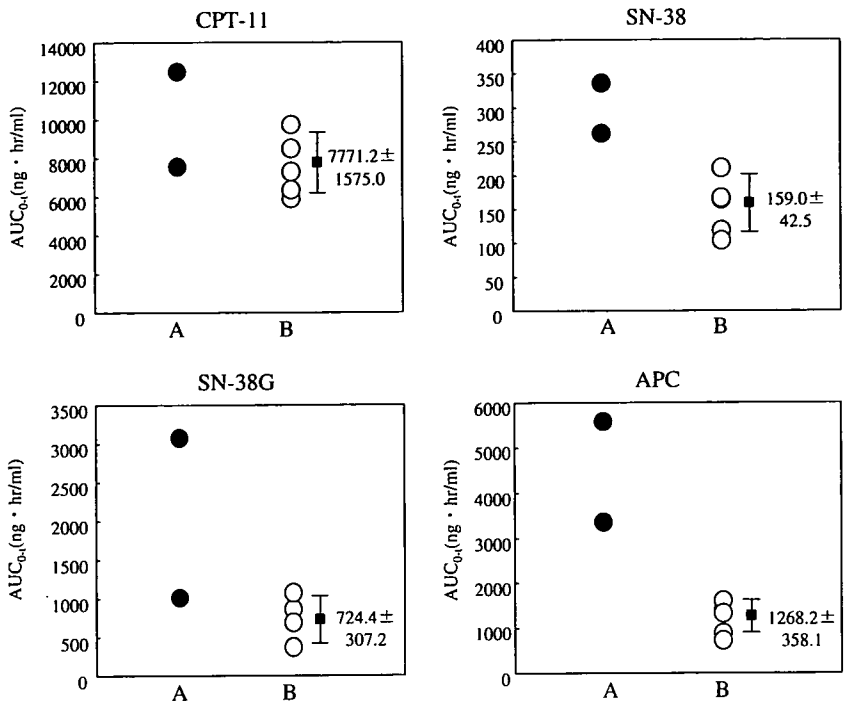

Fig. 2 Area under the concentration versus time curve for irinotecan and metabolites in patients with biliary drainage (*A*, $n = 2$) and without drainage (*B*, $n = 5$). The values are expressed as the mean ± SD

Table 5 Pharmacokinetic parameters after single administration of irinotecan at a dose of 100 mg/m^2 ($n = 7$)

		C_{max} (ng/ml)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-t} (ngh/ml)	CL (l/h m^2)
Irinotecan	A	1,188.5, 1,997.6	1.6, 1.5	7.8, 8.2	7,762, 12,692	11.8, 7.1
	B	1,701.0 ± 348.3	1.5 ± 0.1	7.7 ± 0.9	7,771.2 ± 1,575.0	12.4 ± 2.5
SN-38	A	25.5, 26.2	2.1, 1.5	14.7, 9.9	268, 342	–
	B	17.5 ± 3.8	2.3 ± 0.8	30.2 ± 27.6	159.0 ± 42.5	
SN-38G	A	81.3, 207.2	3.6, 2.0	10.8, 12.5	1,063, 3,130	–
	B	78.8 ± 34.1	2.2 ± 0.2	21.6 ± 13.2	724.4 ± 307.2	
APC	A	309.2, 359.3	2.6, 5.5	7.0, 9.5	3,441, 5,673	–
	B	116.6 ± 39.7	3.0 ± 0.6	8.8 ± 0.7	1,268.2 ± 358.1	

A Patients with biliary drainage $n = 2$

B Patients without biliary drainage (parameters are represented as the mean ± SD) $n = 5$

episodes before onset. Although our study indicated that weekly irinotecan administration would be tolerable in patients with metastatic pancreatic cancer, careful observation is required during the treatment period, since pancreatic cancer patients tend to suffer various tumor-related complications and easily take a turn to the worse because of tumor progression.

There are two studies of single-agent irinotecan that assessed efficacy and toxicity against pancreatic cancer [14, 22]. Sakata et al. [14] studied irinotecan at a dose of 100 or 150 mg/m^2 administered weekly or bi-weekly to previously treated or untreated patients with pancreatic cancer in Japan. Although 57 of 61 enrolled patients were assessable, only 4 patients (7.0%) showed a PR. This study included 28 patients (49.1%) with poor performance status of 2–3 and 22 patients (38.6%) with prior chemotherapy, and no patient showed a PR in these patients with poor performance status or prior chemotherapy. Wagener et al. [22] demonstrated that irinotecan at a dose of 350 mg/m^2 administered every 3 weeks to chemo-naïve pancreatic cancer patients with performance status of ≤ 2, achieved a PR in 3 of 32 assessable patients (9.4%) with an median overall survival of 5.2 months. Although precise reason for the discrepant response rates between our study and the other two studies is unclear, patient background may be one possible explanation because only chemo-naïve patients with good performance status were entered into our study (89.2% of our patients had good KPS of ≥ 90).

For the purpose of the improvement on response rate and prognosis, several studies of combination therapy have been conducted in patients with pancreatic cancer. With regard to irinotecan with gemcitabine, an

encouraging activity, response rates between 20.0 and 24.7% and median overall survival between 5.7 and 7 months, have been reported in two phase II studies [11, 18]. However, survival benefit of this combination therapy was not shown in a phase III study [12], in which, 360 patients were randomized to treatment with a combination of gemcitabine 1,000 mg/m^2 followed by irinotecan 100 mg/m^2 given on days 1 and 8 of a 3-week cycle versus gemcitabine monotherapy. The response rate for the combination therapy was higher at 16.1% compared with 4.4% for gemcitabine alone, but there was no difference in median overall survival (6.3 vs. 6.6 months). However, several clinical studies have recently indicated that irinotecan-based chemotherapy seemed to be an effective treatment for advanced pancreatic cancer after gemcitabine failure: irinotecan–raltitrexed combination demonstrated overall response rate of 16% (3/19) in patients with gemcitabine-pretreated pancreatic cancer [21], and Cantore et al. [3] reported that irinotecan plus oxaliplatin showed response rate of 10% (3/30) with a clinical benefit response of 20% (6/30) for patients with advanced pancreatic cancer after gemcitabine failure.

Because biliary excretion is a major elimination pathway for irinotecan and its metabolites, we investigated the impact of biliary drainage on the pharmacokinetics for this agent. Our results suggested that patients with biliary drainage tended to have higher area under the concentration versus time curve of irinotecan and metabolites compared with patients without biliary drainage. Meyerhardt et al. [10] reported that modest elevation of bilirubin (1.0–1.5 mg/dl) is associated with increased grade 3 to 4 neutropenia in patients treated with irinotecan. The fact that the two patients with biliary drainage in the current study had slight elevation of baseline serum bilirubin level (1.4 and 1.7 mg/dl) might influence pharmacokinetics for irinotecan. Although no severe hematological or non-hematologic toxicities appeared in these two patients, careful observation may be required when treating patients with biliary drainage.

In conclusion, single-agent irinotecan showed a substantial antitumor activity for patients with metastatic pancreatic cancer, rendering a 27.0% response rate. The toxicity with this schedule appears manageable, though it must be monitored carefully.

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Phase II Study of Combination Chemotherapy with Gemcitabine and Cisplatin for Patients with Metastatic Pancreatic Cancer

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Objective: The objectives of this study were to evaluate the efficacy and toxicity of combination chemotherapy with gemcitabine and cisplatin in patients with metastatic pancreatic cancer.
Methods: Patients naïve to chemotherapy who had histologically or cytologically confirmed metastatic pancreatic adenocarcinoma were entered. Gemcitabine was given at a dose of 1000 mg/m^2 over 30 min on days 1, 8 and 15, and cisplatin was given at a dose of 80 mg/m^2 over 150 min on day 1, in 28-day cycles.
Results: A total of 38 patients were enrolled in this study between August 2001 and December 2003. There were no complete responses and 10 partial responses, resulting in an overall response rate of 26% (95% CI: 13.4–43.1%]. Twenty-one patients (55%) had stable disease, whereas 7 (18%) had progressive disease. The median time to progression was 4.2 months and the median overall survival was 7.5 months with a 1-year survival rate of 24%. Grade 3–4 toxicities included neutropenia in 26 patients (68%), thrombocytopenia in 19 (50%), anorexia in 15 (39%) and nausea in nine (24%). There was only one episode of neutropenic fever and there were no significant bleeding episodes or treatment-related deaths.
Conclusion: The combination of gemcitabine and cisplatin administered by this schedule produced a good response rate associated with moderate but manageable toxicities in patients with metastatic pancreatic cancer.

Key words: gemcitabine – cisplatin – phase II study – chemotherapy – pancreatic cancer

INTRODUCTION

Pancreatic cancer currently represents the fifth leading cause of cancer-related mortality in Japan, with an estimated 22 260 deaths attributable to the disease in 2004 (1). Most patients with pancreatic cancer have advanced, unresectable disease at the time of diagnosis and their prognosis is extremely poor. Since a randomized study by Burris et al. in 1997 demonstrated that gemcitabine had a survival benefit versus fluorouracil (2), gemcitabine has been accepted as the standard treatment for advanced pancreatic cancer. However, the median survival of patients with advanced pancreatic cancer treated with single-agent gemcitabine has been only about 6 months (2–4), indicating the pressing need for development of novel treatment strategies.

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Combination of gemcitabine with other agents would be one promising avenue for improving the effect of treatment for advanced pancreatic cancer. In fact, a few recent randomized phase III studies of combinations such as gemcitabine/erlotinib (5) and gemcitabine/capecitabine (6) have demonstrated statistically significant survival benefit in comparison with gemcitabine alone in patients with advanced pancreatic cancer, although there is still no worldwide consensus about the results. As well as these combinations, gemcitabine plus cisplatin has been considered an attractive regimen for pancreatic cancer for several reasons: (i) single-agent cisplatin shows modest activity against pancreatic cancer (7), (ii) preclinical *in vitro* and *in vivo* studies have demonstrated synergistic effects between gemcitabine and cisplatin (8), (iii) the two drugs have non-overlapping, dose-limiting toxicities, and (iv) this combination has demonstrated activity against various malignancies, and is accepted as one of the standard therapies for non-small-cell