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5-Fluorouracil Intra-arterial Infusion Combined With Systemic Gemcitabine for Unresectable Pancreatic Cancer

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Objectives: The aim of this study was to define assessment of response and adverse events of the combination chemotherapy of 5-fluorouracil (5-FU) pancreatic and hepatic arterial continuous infusion and systemic gemcitabine administration for unresectable pancreatic cancer.

Methods: We treated 24 chemotherapy-naive patients with unresectable pancreatic cancer. To prevent gastroduodenal injury from 5-FU infusion, the catheter was placed to allow the distribution of 5-FU to the pancreatic tumor and the liver after occlusion of the gastric and pancreaticoduodenal arteries. 5-FU was administered at a dose of 250 mg/d on days 1 to 5 every week as a continuous arterial infusion. Gemcitabine was infused intravenously at a dose of 1000 mg once weekly for 3 consecutive weeks of every 4 weeks.

Results: The partial response rate was 20.8% (5 of 24), although there was no case of complete response. Fourteen cases (58.3%) were stable disease, and 5 cases (20.8%) were progressive disease. The most common toxicities were hematological and gastrointestinal events. No patients died of adverse effects using this chemotherapy. Gastric and/or duodenal ulcers occurred because of 5-FU intra-arterial infusion. Catheter-related cholangitis occurred in patients with biliary drainage for obstructive jaundice. Median survival time was 14 months, with a 50.9% 1-year survival rate, although patients with performance status 2 and multiple organ metastases had a poor prognosis.

Conclusions: This combination chemotherapy was well tolerated and seemed to be effective for patients with unresectable pancreatic cancer.

Key Words: 5-fluorouracil intra-arterial infusion, distant metastases, unresectable pancreatic cancer

(*Pancreas* 2005;30:223–226)

Received for publication August 10, 2004; accepted December 22, 2004.
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Cancer of the pancreas has increased in incidence over the past several decades.[1] Despite improvements in imaging technology, less than 20% cases are potentially resectable at the time of initial diagnosis.[2] Unfortunately, most patients have locally advanced or metastatic diseases. For advanced cases, the 5-year survival rate is less than 1%, with most patients dying within 1 year of diagnosis. Gemcitabine has served as the standard of chemotherapy, based on its clinical benefit and improved survival in a phase 3 trial.[3] Moreover, the action of gemcitabine seems to be synergetic with 5-fluorouracil (5-FU).[4] In addition to this fact, the intra-arterial infusion of antineoplastic agents gives higher concentrations to the targeted part compared with whole body administration and is associated with lower toxicity.

The primary endpoint of this study was the objective response rate. Secondary endpoints studied included characterization of the toxicity profile and median survival.

PATIENTS AND METHODS

Patients Selection

Between January 2001 and January 2004, we treated 24 chemotherapy-naive patients with unresectable pancreatic cancer. Locally advanced or metastatic adenocarcinoma of the pancreas was histologically or cytologically confirmed in 11 patients. To be included in this study, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2, including the following: absolute neutrophil count ≥1500/mm^3, bilirubin ≥1.5 mg/dL, aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels ≤3 times the upper limit of normal, and creatinine ≤2 mg/dL. All patients were advised of the investigational nature of the study and gave written informed consent to participate before the study.

Catheter Implantation

A 5-Fr catheter was inserted from the femoral artery with the Seldinger technique. The right and left gastric arteries and the anterior and posterior superior pancreaticoduodenal arteries were occluded by microcoils to prevent gastroduodenal injury from 5-FU infusion and to simplify blood flow to the pancreas and liver. Under local anesthesia, the catheter for arterial infusion was introduced from the branch of the left subclavian artery in 14 cases and from the femoral artery in 10 cases. After the closure of the distal tip of the catheter, a side hole was made at an appropriate site in the celiac axis to allow

the distribution of 5-FU to both the pancreatic tumor and the whole liver. An arterial port was implanted in the subcutaneous tissue.

Drug Administration

Gemcitabine diluted in normal saline was infused intravenously for 30 minutes at a dose of 1000 mg once weekly for 3 consecutive weeks of every 4 weeks. 5-FU was administered at a dose of 250 mg/d on days 1 to 5 every week as continuous infusion through the arterial port. One cycle length was defined as 4 weeks. In case of grade 2 or more toxicity according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0, drug infusion was interrupted until recovery. Patients were allowed to remain on treatment providing there was no evidence of progressive disease and/or PS ≥3. Complete blood counts (CBCs) were repeated weekly before infusion of the drugs. Chemistry profiles were performed every month.

Pretreatment and Follow-up Evaluations and Assessment of Response Rate

A history and physical examination were performed before this study and before each infusion. Studies included CBC, serum AST, ALP, total bilirubin, creatinine, sodium, potassium, and glucose. Computed tomography for response evaluation was performed every 4 weeks. The therapeutic responses were evaluated according to World Health Organization criteria. A complete response (CR) was defined as the complete disappearance of all assessable disease for at least 4 weeks. A partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the bidimensional diameters of measurable lesions for at least 4 weeks. Stable disease (SD) was defined as the decrease of less than 50% or the increase of less than 25% in tumor size. Progressive disease (PD) was defined as an increase of at least 25% or appearance of new neoplastic lesions.

Toxicity and Survival Evaluation

This study used the NCI-CTC version 2.0 adverse event monitoring and reporting. Toxicity was evaluated before each cycle of treatment. The maximum grade for each type of toxicity was recorded.

In all patients, the date of initial treatment was chosen as the starting point for survival analysis. Overall survival was determined from day 1 of treatment until death. The survival curve was drawn with the Kaplan-Meier method.

RESULTS

Patients Characteristics

The characteristics of the 24 patients are outlined in Table 1. Sixteen of the patients were men and 8 were women, with a median age of 62.6 years (range, 42–76 years). The primary pancreatic lesion was located in the head in 12 patients, in the body in 9 patients, and in the tail in 3 patients. Of the 24 patients, 21 patients (87.5%) had distant metastases. The most common site of metastases was the liver (17 patients). Three patients suffered from multiple organ metastases. Nine patients had a PS of 0. Ten patients had a PS of 1. Five patients had a PS of 2. Patients received a minimum of 3 cycles and a maximum of 12 cycles.

TABLE 1. Patients Characteristics

No. of patients	24
Age (yr)	
Median	62.6
Range	42–76
Male/female	16/8
ECOG performance status	
0	9
1	10
2	5
Site of primary lesion	
Head	12
Body	9
Tail	3
Site of metastases	
None	3
Liver	17
Dissemination	1
Multiple	3

Toxicity

Hematological and nonhematological toxicities related to therapy are outlined in Table 2. No potentially life-threatening toxicity was seen. The most common toxicities were hematological and gastrointestinal events. All patients had leukopenia, which abated after discontinuation of drug infusion. One patient developed grade 4 neutropenia, which also abated after interruption of drug infusion. Eighteen patients had anemia during treatment. Two of 3 patients with grade 3 anemia required blood transfusion. Thrombocytopenia was mild and occurred in 8 patients (30%). Toxicities distinctively related to 5-FU arterial infusion were gastric and/or duodenal ulcer (4 patients). Gastric and/or duodenal ulcer was healed by treatment with antiulcer agents and discontinuation of 5-FU intra-arterial infusion. Catheter-related

TABLE 2. Treatment-related Toxicities for This Combination Therapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	8	6	4	0
Leukopenia	5	13	6	0
Neutropenia	4	7	7	1
Thrombocytopenia	6	2	0	0
Gastrointestinal				
Nausea	9	6	0	0
Gastric/duodenal ulcer	0	4	0	0
Others				
Cholangitis	0	2	3	0
Cerebral infarction	1	0	0	0

Values are numbers of patients.

cholangitis occurred in 5 patients who had biliary drainage for obstructive jaundice and were treated by appropriate exchange of the drainage tube. One patient experienced mild cerebral infarction with partial defect of the visual field. Another patient experienced dislocation of the infusion catheter, which required reimplantation of the catheter.

Therapeutic Response and Outcome

The PR rate was 20.8% (5 of 24), although there was no case of CR. Fourteen cases (58.3%) were SD, and 5 cases (20.8%) were PD.

The overall survival curve is depicted using the Kaplan-Meier method in Figure 1. The median overall survival was 14 months. Survival at 6, 12, and 24 months was 83.3%, 50.9%, and 12.7%, respectively. Five patients, who obtained PR during the follow-up period, had been alive more than 15.3 months at the time of data analysis (range, 15.3–25 months). Patients with a PS of 0 to 1 have survived significantly longer than patients with a PS of 2 (Fig. 2). Patients with a PS of 2 had a poor survival (4.5–7.9 months). All patients without distant metastases were alive more than 1 year. On the other hand, all patients with multiple distant metastases died within 1 year (range, 4.5–12 months; Fig. 3). No patients died as a result of adverse effects of chemotherapy. PS did not change during treatment until the progression of diseases.

DISCUSSION

The primary endpoint of this trial was the objective response with secondary endpoints of safety and median survival. The expected goal was to identify the efficacy of this combination chemotherapy for survival benefit for unresectable pancreatic cancer.

The response rate was 20.8% in our study, which is compatible with that in another trial with the same combination chemotherapy in patients with pancreatic and biliary tract cancer (25%).[5] Gemcitabine has shown antitumor activity in patients with carcinoma of the pancreas and is widely used as first-line chemotherapy in the treatment of this disease. However, despite superior activity compared with 5-FU, the result achieved with single-agent gemcitabine in pancreatic cancer is still poor (reported response rate of 5.4%, a median survival time of 5.65 months, and a 1-year survival rate of 18%).[3] It is thus indicated that the addition of 5-FU intra-arterial infusion to systemic gemcitabine might have efficacy compared with gemcitabine alone. To our knowledge, other combinations of intra-arterial and systemic chemotherapy have not been reported in patients with unresectable pancreatic cancer.

The rationale for intra-arterial infusion of chemotherapeutic agents seems to be promising from the point of view of the drug's concentration-response, because most liver metastases (>3 mm) have an arterial blood supply.[6,7] Moreover, intra-arterial infusion is considered to take advantage of the first pass effect of the drug, generating higher local drug concentrations at tumor cells with a lower toxicity. Continuous intra-arterial infusion may be advantageous in maintaining the

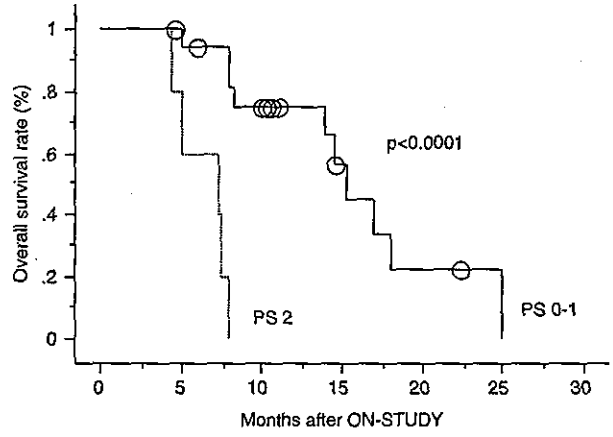

FIGURE 2. Kaplan-Meier survival curves for patients with PS 0-1 or PS 2. $P < 0.001$ (log-rank test).

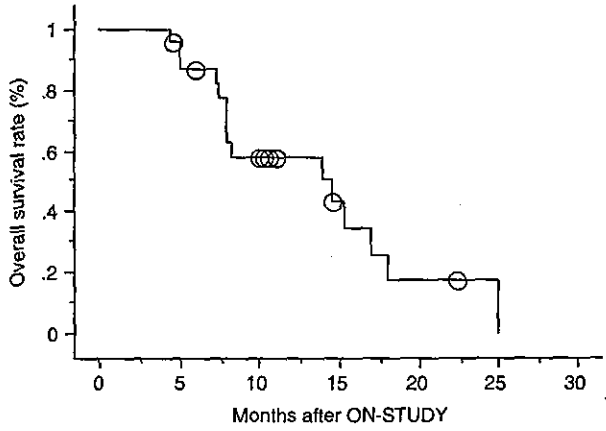

FIGURE 1. Overall survival for patients receiving 5-FU intra-arterial infusion and systemic gemcitabine for unresectable pancreatic cancer.

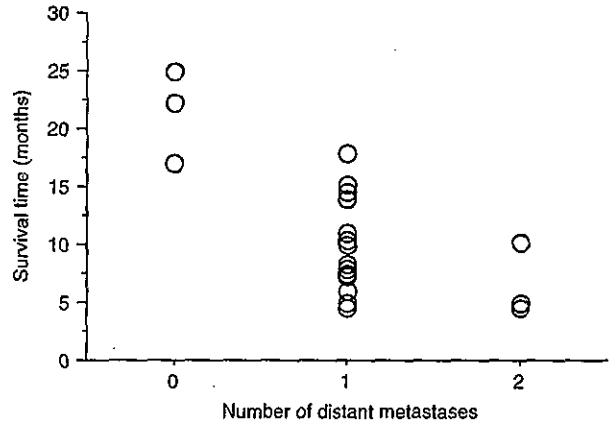

FIGURE 3. Relationship between survival time and number of distant metastases.

concentration of time-dependent chemotherapeutic agents such as 5-FU. On the other hand, systemic blood concentration of 5-FU may be insufficient to treat occult extrahepatic metastases, because 5-FU has a high hepatic first-pass effect of up to 50%.[8] Although no evidence of an advantage in progression-free survival or overall survival of the intra-arterial infusion compared with systemic therapy was reported for colorectal liver metastases,[9] a significantly higher response rate has been reported.[10] Pancreatic and hepatic arterial infusion chemotherapy for pancreatic cancer may not be enough, because extraabdominal metastases were documented in 27% of patients, even after curative resection of pancreatic carcinoma.[11] Therefore, we believe systemic chemotherapy with gemcitabine combined with regional and hepatic intra-arterial infusion may be necessary for the treatment of pancreatic cancer.

This combination chemotherapy was well tolerated in all patients. Patients could receive a maximum of 12 cycles. There were no potentially life-threatening adverse events. Most toxicities were mild hematological events. Patients experienced grade 3 or 4 anemia (16.7%), leucopenia (25.0%), and neutropenia (33.3%). One adverse effect of 5-FU intra-arterial infusion was gastric and/or duodenal ulcers. Before introducing coil embolization of gastric and duodenal arterial branches, we previously experienced duodenal obstruction caused by duodenal edema or gastric inflammation. Although duodenal obstruction did not occur in this study, gastric and/or duodenal ulcer still occurred. Prevention of gastroduodenal injury from 5-FU infusion might be difficult even after coil embolization of gastric and duodenal arterial branches. Cholangitis is an adverse effect specific to patients with obstructive jaundice. Special attention needs to be paid to patients with obstructive jaundice, because chemical cholangitis caused by 5-FU infusion aggravates inflammation. In 4580 cases of hepatic artery infusion by Barnett et al,[12] the most common toxicities included gastrointestinal symptoms in 22%, chemical hepatitis in 19%, and bone marrow toxicities in 8%. Catheter implantation was radiologically performed in this study. Another problem associated with intra-arterial infusion chemotherapy is catheter-associated complications. According to Heinrich et al,[13] catheter-associated complications occurred in 4% to 56% of cases. In this trial, 1 patient (4.2%) suffered from mild cerebral infarction as a catheter-related complication.

This trial showed that the combination of regional 5-FU intra-arterial infusion and systemic gemcitabine was effective for unresectable pancreatic cancer, with a median survival time of 14 months and a 1-year survival rate of 50.9%. However, patients with a PS of 2 had poor survival. Moreover, patients with multiple distant metastases also died within 1 year. Therefore, this combination chemotherapy may not be indicated for patients with a PS of 2 and/or multiple distant metastases.

There are several limitations in this study. This was a nonrandomized study with a small series of 24 patients. Adenocarcinoma was pathologically confirmed in 11 patients. Moreover, we adopted "milligrams per body" instead of "milligrams per square meter" for doses of these drugs. Because the study was a preliminary one, we mainly focused on feasibility of the clinical protocol. However, it is necessary to plan a randomized control study to clarify the efficacy of this combination chemotherapy for survival benefit against only systemic chemotherapy in the future. Doses of drugs should be determined in proportion to body dimensions. Pathologic confirmation in all patients is required before enrollment onto a clinical study.

In conclusion, this combination chemotherapy was well tolerated and seemed to be effective for patients with unresectable pancreatic cancer. Moreover, this combination chemotherapy should be assessed as an adjuvant chemotherapy after curative operation to improve survival.

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Reprinted from
Jpn J Clin Oncol 2004;34(12)717–721
doi:10.1093/jjco/hyh138

Individual Patient-level and Study-level Meta-analysis for Investigating Modifiers of Treatment Effect

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Jpn J Clin Oncol 2004;34(12)717–721
doi:10.1093/jjco/hyh138

Original Articles

Individual Patient-level and Study-level Meta-analysis for Investigating Modifiers of Treatment Effect

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Received May 31, 2004; accepted October 6, 2004

Background: In meta-analyses of clinical trials, clinicians are often interested in examining subset effects. Meta-regression of aggregated data is a usual approach for relating sources of variation in treatment effects to specific study characteristics. However, it is known that study-level analyses can lead to biased assessments and have some limitations in explaining the heterogeneity. An individual patient data (IPD) meta-analysis offers several advantages for this purpose.
Methods: We compared some regression analyses of IPD with meta-regression analyses of the summarized data using a real-world example in order to investigate whether a binary patient characteristic is related to treatment effect. We used data from 10 randomized trials for non-small-cell lung cancer ($n = 1355$).
Results: For treatment × stage interaction in IPD regression analysis, none of the tests of interactions was statistically significant. The meta-regression analysis gave a greater *P*-value than the IPD analysis. When excluding two studies, which had only stage I patients, the interaction was also not statistically significant in IPD analysis. On the other hand, the result of meta-regression analysis, though also showing no significant relationship, revealed a clear reversal in the direction of effect.
Conclusion: We suggest that the results of meta-regression analyses would not be as robust as those of regression analyses using IPD in examining potential modifiers of treatment effects. To investigate whether patient characteristics are related to treatment effects, we suggest that interaction tests and sensitivity analyses using IPD should be employed whenever possible.

Key words: meta-analysis – heterogeneity – meta-regression – individual patient data – interaction test

INTRODUCTION

Meta-analysis is a tool in the continual process of clinical research for the discovery of new knowledge and also a scientific basis for planning future research. Assessment of between-study heterogeneity is one of the prime values of meta-analysis from this standpoint (1,2). Although some statistical models such as random-effects models account for heterogeneity to estimate a summary effect measure, they do not provide a method of exploring the reasons why study results vary. Heterogeneity between results from various clinical studies may occur, for instance, when patient populations vary across them or when patient characteristics are related to treatment effects.

Meta-regression of aggregated data is the usual approach in relating sources of variation in treatment effects to specific study characteristics (3). Meta-regression is a regression analysis in which the study estimates of treatment effect are the response variables, while study-level covariates, each of which has a value defined for each study, are the explanatory variables. For example, meta-regression analysis was undertaken to explore differences in graft-versus-host disease (GVHD) incidence between peripheral blood stem cell transplantation (PBSCT) and bone marrow transplantation (BMT) (4). In a cancer epidemiology study, the effects of alcohol and tobacco on the upper aerodigestive cancers were examined using the meta-regression technique (5). However, it is known that

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study-level analyses can lead to biased assessments, and use of aggregated summary values has some limitations for explaining the heterogeneity (6–8). An individual patient data (IPD) meta-analysis offers several advantages for this purpose. Our goal is to compare some regression analyses of IPD with meta-regression analyses of the summarized data using a real-world example, in order to investigate whether a binary patient characteristic is related to treatment effect. We specifically address the circumstance when an entire study may be homogeneous with respect to a level of a categorical covariate, i.e. the study includes patients only in one category of a categorical covariate.

METHODS

DATA

Using data from the randomized trials for investigating the efficacy of adjuvant immunochemotherapy (a streptococcal preparation, OK-432) after resection of non-small-cell lung cancer, we sought to examine whether the stage of diseases, which was categorized into stage I or stage II–IV, was related to treatment effect. The patient data were collected from 10 randomized trials from the meta-analysis reported by Sakamoto et al. (9). The patient data of study no. 5 were not available because the trial was conducted in Yugoslavia. The size of the analysis set and the number of events in the present analysis were slightly different from the reported literature-based meta-analysis because of the availability of data and timing of the analysis. In these trials, the primary end-point was overall survival and the median follow-up time was 4.9 years.

The summarized results and characteristics of the studies are shown in Table 1, using a hazard ratio of death as a summary of the results in each study. Four patients in study no. 8 with missing values for the stage of disease were excluded. A total of 1355 subjects (treatment group, 686; control group, 669) were included in the present analysis. Two studies (study nos 2 and 10) had patients exclusively with stage I.

The overall effects were estimated using the Cox proportional hazards model stratified by the study (10). The overall treatment effect was statistically significant [hazard ratio 0.80, 95% confidence interval (CI) 0.69–0.93]. The test for heterogeneity in the log-hazard ratio across studies yielded $\chi^2(9) = 14.9$ ($P = 0.094$), and this indicated that the null hypothesis of no heterogeneity in the log-hazard ratio cannot be rejected at the 0.05 level of significance. In subgroup analysis according to the stage of disease, there was a statistically significant treatment effect among patients with stage I ($n = 740$; hazard ratio 0.71; 95% CI 0.55–0.92). On the other hand, no significant treatment effect was observed in patients with stage II–IV ($n = 615$; hazard ratio 0.86; 95% CI 0.71–1.04).

INDIVIDUAL PATIENT-LEVEL ANALYSIS

To evaluate treatment × stage interaction in the IPD regression analysis, we considered two types of regression models. Let subject i be a member of study j, $j = 1, \ldots, k$ ($k = 10$), which follows a stratified Cox regression model (10). The hazard function for subject i in study j can be written as

$$\text{Model 1: } \lambda_{ij}(t) = \lambda_{0j}(t)\exp\left\{\beta_1 \text{treat}_{ij} + \beta_2 \text{stage}_{ij} + \beta_3(\text{treat} \times \text{stage})_{ij}\right\}$$

where $\lambda_{0j}(t)$ is the baseline hazard for subjects in study j, treat_{ij} is coded 0 for the control group and 1 for the treatment group, stage_{ij} is coded 0 for stage I and 1 for stage II–IV, and $(\text{treat} \times \text{stage})_{ij}$ is the treatment by stage interaction. Their

Table 1. Data from 10 randomized trials of non-small cell lung cancer

Study*	Treatment group		Control group		Hazard ratio (95% CI)	Percentage of patients with stage II–IV
	Deaths	Patients	Deaths	Patients		
1	71	112	82	105	0.62 (0.45–0.86)	62.2
2	17	46	23	48	0.74 (0.40–1.38)	0.0
3	18	36	29	42	0.57 (0.32–1.03)	64.1
4	25	45	22	36	0.86 (0.48–1.52)	53.1
6	25	52	26	51	0.90 (0.52–1.57)	50.5
7	23	43	18	37	1.36 (0.73–2.52)	57.5
8	42	80	41	74	0.82 (0.54–1.27)	51.9
9	73	174	76	178	1.11 (0.81–1.53)	43.2
10	5	36	15	37	0.31 (0.11–0.84)	0.0
11	21	62	29	61	0.68 (0.39–1.20)	46.3
Total	320	686	361	669	0.80 (0.69–0.93)	45.4

*The references of the original studies are provided in Sakamoto et al. (9)

corresponding regression coefficients are β_1, β_2 and β_3. In model 1, $e^{\beta 1}$ means the hazard ratio for treatment effect in stage I, $e^{(\beta 1 + \beta 3)}$ means the hazard ratio for treatment effect in stage II–IV, and $\beta_3 = 0$ means no difference in treatment effect between stages. The analysis based on model 1 is the most common approach for carrying out IPD meta-analysis for survival data. Thus, model 1 is regarded as a reference model in terms of the validity of the results.

To compare with the meta-regression analyses using summary data, which had risk ratio as its measure of effect, we changed the response variable from survival time to a binary outcome, i.e. alive or dead at the end of study, because information on the number of those alive or dead at a fixed time might be the only data available in any selected literature for meta-analysis. We used exponential risk models to examine interactions between the treatment and the stage of disease. The fixed-effects model can be written as

$$\text{Model 2: } \log(P_{ij}) = \alpha\ \text{study}_j + \beta_1\ \text{treat}_{ij} + \beta_2\ \text{stage}_{ij} + \beta_3(\text{treat} \times \text{stage})_{ij}$$

where P_{ij} is the risk of death for subject i in study j. The model has a binomial distribution and log link function. In model 2, $e^{\beta 1}$ means the risk ratio for treatment effect in stage I, $e^{(\beta 1 + \beta 3)}$ means the risk ratio for treatment effect in stage II–IV, and $\beta_3 = 0$ means no difference in treatment effect between stages.

Study-level Analysis

In the study-level analysis, we assumed that the only information available is the number alive or dead at the end of study and aggregated covariate data. The meta-regression model using summary data can be written as:

$$\text{Model 3: } \log(RR_j) = \alpha_0 + \alpha_1 z_j$$

where RR_j is the risk ratio in study j, and z_j is the proportion of stage II–IV in study j. The parameters were estimated by weighted least squares regression of $\log(RR_j)$ on z_j with weights $w_j = 1/v_j$ where v_j is the variance of the $\log(RR_j)$ (11). All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Comparison of Methods

The results of the IPD analyses are shown in Table 2. In model 1, the estimated hazard ratio for treatment effect in stage I (the estimates for $e^{\beta 1}$) was 0.72, the estimated hazard ratio for treatment effect in stage II–IV (the estimates for $e^{(\beta 1 + \beta 3)}$) was 0.85, and the estimated interaction term (β_3) was 0.169. In model 2, the estimated risk ratio for treatment effect in stage I (the estimates for $e^{\beta 1}$) was 0.77, the estimated risk ratio for treatment effect in stage II–IV [the estimates for $e^{(\beta 1 + \beta 3)}$] was 0.91, and the estimated interaction term (β_3) was 0.172. In the regression models using IPD, none of the tests of treatment × stage interactions was statistically significant. These results indicated that the treatment effect might not be different between stage I patients and stage II–IV patients.

Table 2. Regression estimates from regression analyses using individual patient data

Model	Main effect of treatment		Main effect of stage		Interaction between treatment and stage	
	β_1	*P*-value	β_2	*P*-value	β_3	*P*-value
1	−0.327	0.011	1.126	<0.001	0.169	0.293
2	−0.268	0.010	0.645	<0.001	0.172	0.134

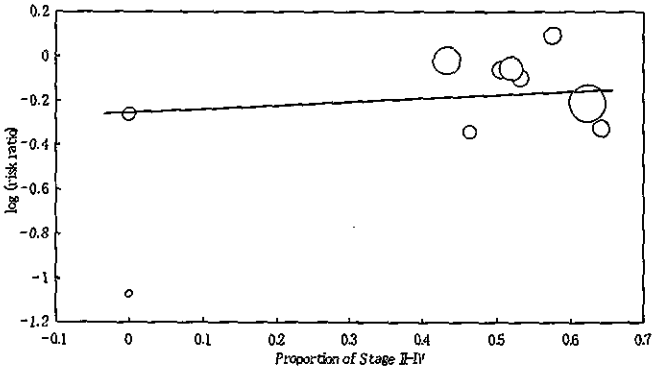

Figure 1. Meta-regression of treatment effect versus proportion of stage II–IV for 10 trials.

Figure 1 shows a bubble plot of the log-risk ratio against the proportion of patients with stage II–IV. A bubble shows a study and the size of bubble is proportional to the inverse of the variance of the log-risk ratio. The meta-regression analysis using summary data gave a greater *P*-value than model 2, which are models for log-risk ratio (slope, 0.20; standard error of the slope, 0.35; $P = 0.568$).

Sensitivity Analysis

When excluding two studies (study nos 2 and 10), both of which were only on stage I patients, we found that the interaction term was also not statistically significant in any models (Table 3). The *P*-value for interaction tests was larger than the overall results. The estimated treatment effects in stage I patients (the estimates for $e^{\beta 1}$) were 0.78 and 0.82 in model 1 and model 2, respectively. They were slightly smaller after removing the two studies than before removing them. In stage II–IV patients, the estimates of the treatment effect (the estimates for $e^{(\beta 1 + \beta 3)}$) were 0.85 and 0.91 in model 1 and model 2, respectively, and they remain unchanged.

On the other hand, the direction of the effect from the meta-regression analysis was dramatically altered (slope, −0.86; standard error of the slope, 0.70; $P = 0.218$) with no significant relationship between the treatment effect and the stage (Fig. 2). The point estimate of the slope was changed from positive to negative after excluding two studies.

Table 3. Regression estimates from regression analyses using individual patient data, excluding study nos 2 and 10

Model	Main effect of treatment		Main effect of stage		Interaction between treatment and stage	
	β_1	*P*-value	β_2	*P*-value	β_3	*P*-value
1	−0.250	0.090	1.161	<0.001	0.092	0.601
2	−0.199	0.096	0.675	<0.001	0.103	0.424

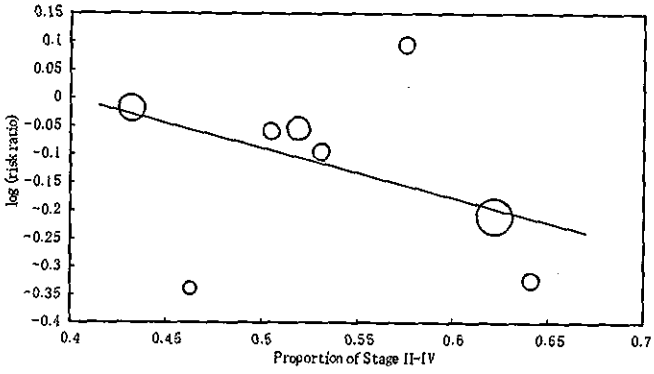

Figure 2. Meta-regression of treatment effect versus proportion of stage II–IV from eight trials, excluding study nos 2 and 10.

DISCUSSION

Investigating potential sources of heterogeneity is an important component of carrying out a meta-analysis. The underlying level of risk can surface as a key variable related to a given treatment effect (12). In the present study, we focused on the stage of disease as a candidate of a treatment effect modifier because disease stage is one of the most important prognostic factors in any cancer. In the conventional subgroup analysis according to the stage, there was a statistically significant treatment effect among patients with stage I. On the other hand, there was no significant effect in the patients with stage II–IV. Some reports emphasize that an inappropriate subgroup analysis may lead to an incorrect conclusion (13,14). They recommended that statistical tests of interaction should be used rather than inspection of subgroup *P*-values. Therefore, we performed the interaction tests using Cox regression models and exponential risk models.

In cases where no individual patient data are available, meta-regression of summary data has been used to investigate heterogeneity of treatment effects. For example, Cutler et al. showed a fitted equation for the relationship between the relative risk of GVHD and the difference in number of T cells; however, the relationship did not reach statistical significance (4). In the meta-regression analysis, only five studies were included and the sample size per study ranged from 37 to 350. We also showed using an example that study-level meta-analysis has lower power than an equivalent IPD analysis. With regard to the statistical power for investigating heterogeneity of treatment effects in various situations, Lambert et al. performed a simulation study for meta-analyses including five, 10 and 20 studies, each of 200, 500 and 1000 patients (6). In the case of 10 studies of size 200 with a small effect size, 21% of the IPD meta-analyses are significant at the 5% level, while only 7% are significant for the meta-regression. They showed that the IPD analyses have greater power for any of the simulated situations. The intra-class correlations are consistently low (range 0.06–0.22), indicating that there is little agreement between the two methods. Even if appropriate statistical methods have been used for meta-regression, there are a number of limitations to the interpretation of the results (8,15).

As we have shown in the present study, for categorical covariates, one of the limitations is potential confounding across studies. In our example, two studies (study nos 2 and 10) have no information concerning the difference of treatment effects between stage I and stage II–IV, because these studies only have stage I patients. The result of meta-regression were changed if we use all the information (11 studies), or if we use only information within studies (nine studies). Therefore, we should always interpret the results while considering this kind of confounding between covariates and studies. Another major drawback of meta-regression is aggregation bias or ecological fallacy (11,16). The fallacy is the mistaken assumption that a statistical association observed between two group-level variables is equal to the association between the corresponding variables at the individual level. If we have no individual patient data, analysis using only published average data could be difficult to interpret, because a between-study relationship based on aggregated data might not reflect a within-study relationship based on IPD.

In conclusion, we suggest that the results of meta-regression analyses using summary data would not be as robust as that of regression analyses using IPD to examine potential modifiers of treatment effect. To investigate whether patient characteristics are related to treatment effects, we suggest that interaction tests and sensitivity analyses using IPD should be employed whenever possible.

Acknowledgments

This paper was presented in part at the 1st US–Japan Biostatistics Workshop, Kobe, September 26, 2003. We would like to thank the Japanese Meta-Analysis Group in Cancer of the Japanese Society of Strategies for Cancer Research and Therapy, and Chugai Pharmaceutical Co. Ltd for permission to use the valuable data.

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Epidemiological Characteristics of HIV and AIDS in Japan based on HIV/AIDS Surveillance Data : An International Comparison

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Reprinted from
The Journal of AIDS Research
Vol. 6 No. 3 August 2004
Published by
The Japanese Society for AIDS Research

Research Report

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Objective : The aim of this study was to compare the annual trends in the reported number of Japanese HIV/AIDS cases, and the distribution of sex, age and route of infection. The increasing trend of reported AIDS cases at the onset of the Japan epidemic was also compared with those of other industrialized countries.

Materials and Methods : HIV/AIDS surveillance data through December 2001 were utilized. As for the comparison of increasing trends at the onset of the epidemic, the Epidemiological Facts Sheets organized by the UNAIDS/WHO (United Nations Programme on AIDS/World Health Organization) were used. Nine industrialized countries, the USA, EU (European Union) (51 countries of the WHO European Region), Canada, Australia, UK, Germany, Italy, Spain, and France were selected for comparisons.

Results : Comparisons of Japanese HIV/AIDS with other industrialized countries revealed that the annual trend in reported cases was still increasing. The proportion of people with HIV aged 40 or above was high, and the proportion of males with HIV infected through heterosexual contact was extremely high. The increasing trend in reported AIDS cases at the onset of the Japan epidemic was extremely slow compared to that in other countries. In particular, there were differences in the number of cases infected through MSM (men who have sex with men), including bisexual contact, and or IDU (injecting drug use).

Conclusion : The epidemiological characteristics of HIV/AIDS in Japan, such as annual trends, and the distribution of sex, age and route of infection were revealed by comparisons with the surveillance data from nine other countries.

Key words : HIV, AIDS, surveillance, international comparison

The Journal of AIDS Research 6 : 184-193, 2004

Introduction

HIV/AIDS surveillance systems have been established in many countries[1-5] to estimate the prevalence and incidence of HIV/AIDS. They have provided some of the most important data available for determining the course of the epidemic and identifying high-risk population subgroups.

In Japan, HIV/AIDS surveillance has been fully operational since 1984, and several studies have been conducted to facilitate the interpretation and understanding of the surveillance data[6-14]. In particular, trends in the number of reported HIV/AIDS cases[7-9,11] and reported deaths[12], the issues related to reporting delays[9,11], estimations of the coverage rate of reported individuals with HIV[7,9,11], and future predictions of the number of people with HIV and AIDS[6,13], have been investigated in detail. However, only few studies have tried to

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Received December 11, 2003 ; Accepted July 26, 2004

compare the characteristics of Japan's epidemic with those of the industrialized countries that first encountered the HIV epidemic. Umeda *et al.*[14] compared the epidemiological characteristics of Japanese AIDS cases infected through heterosexual contact with those of the UK (United Kingdom) and the USA (United States of America) based on surveillance data through 1996. Although the number of people with HIV and AIDS in Japan is still low compared to other industrialized countries, it is important to internationally examine the similarities and/or differences in the epidemiological characteristics of HIV/AIDS in Japan.

In this study, after examining the situations for surveillance systems in other industrialized countries, we compared the annual trend in the reported number of Japanese HIV/AIDS cases, and the distribution of sex, age and route of infection with those of other industrialized countries based on available HIV/AIDS surveillance data through December 2001. The increasing trends in reported AIDS cases at the onset of the epidemic in each country were also compared.

Materials and Methods

HIV/AIDS surveillance in Japan

AIDS surveillance in Japan began in 1984 and was legalized through the implementation of the "Act of AIDS Prevention" in 1989[10,15]. Following enactment of the "Law Concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases" in 1999, the "Act of AIDS Prevention" was abolished and AIDS surveillance was integrated into the "National Epidemiological Surveillance of Infectious Diseases" organized by the Ministry of Health, Labor and Welfare, Japan.

Both AIDS and HIV infections are notifiable conditions and must be reported to the Public Health Center authorities by the diagnosing physician within 7 days. Each Public Health Center reports the information to the Prefectural/Municipal City Health authorities and the Infectious Diseases Surveillance Center (IDSC) through an online system. Two types of notification forms were created : the First Report is utilized when a physician has identified an HIV-positive case or AIDS case for the first time, and the Second Report is used when a physician has recognized a change in the pathological status of a case, such as from HIV-positive to AIDS or from AIDS to death. It should be noted that filing the Second Report was changed to be optional under the "Law Concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases". Both reports are examined and approved every three months by the AIDS Surveillance Committee of the Ministry of Health, Labor and Welfare, Japan. Cases caused by blood-derived coagulation products are not reported.

AIDS notification must indicate the distinction between HIV-positive and AIDS, nationality, route of infection, sex, age at diagnosis, suspected place of infection (in Japan/abroad), place of residence, diagnosis method, symptoms at diagnosis, AIDS indicator diseases, and the date of first HIV or AIDS infection, diagnosis and reporting. The Second Report includes the nationality, sex, age at diagnosis, the date of HIV or AIDS diagnosis and reporting, and any additional information describing the changes that have occurred and the date of occurrence. Neither report includes information regarding the name, address, or date of birth of the patient or any notes that might lead to personal identification.

Surveillance data and analysis method

The number of people reported with HIV or AIDS was calculated based on the annual report of HIV/AIDS surveillance in Japan[5]. Only Japanese individuals with HIV and AIDS were included in this study, because there are known differences in the epidemiological characteristics such as the trend in the number of reported cases, distribution of sex and route of infection between Japanese and non-Japanese residents of Japan[8,11]. The cumulative reported number of HIV and AIDS cases among the Japanese through 2001 were 2915 and 1654, respectively. Note that the reported number of AIDS cases does not include the cases from the Second Report after April 1, 1999, as stated above.

Nine industrialized countries/regions, the USA[1], EU (European Union, 51 countries of the WHO European Region)[2], Canada[3], Australia[4], UK[16], Germany[17], Italy[18], Spain[19], and France[20] were selected for comparisons between countries. About 80% of the AIDS cases reported in the HIV/AIDS Surveillance of Europe[2] conducted by the European Centre for Epidemiological Monitoring of AIDS (EuroHIV programme) occurred in five of the selected countries; UK, Germany, Italy, Spain, and France.

The number of people reported with HIV and AIDS by sex, age, route of infection, and the calendar year of diagnosis was calculated based on the annual HIV/AIDS surveillance report from each country through December 2001. Because the surveillance reports from Australia and France did not include the number of cases according to age category, age

distribution was not evaluated in these two countries. Regarding HIV infection, only 6 countries/regions were used in these comparisons because HIV surveillance was not conducted in France or throughout Spain and Italy where information on sex, age, and route of infection was unavailable.

The definition of an AIDS case was the presence of indicator diseases such as *Pneumocystis carinii* pneumonia, pulmonary tuberculosis, or oesophageal candidiasis, as well as a positive HIV test. Although in 1993, the case definition was expanded in the USA to include HIV-infected persons with CD4+ T-lymphocyte counts less than 200 per μl or a CD4+ percentage less than 14, the other criteria were essentially the same between all countries/regions and Japan.

Route of infection was divided into six categories : heterosexual contact (male), heterosexual contact (female), men who have sex with men (MSM), including bisexual contact, injecting drug use (IDU), other routes, and risk not reported or identified. The category of "other routes" comprises mother-to-child infection, blood transfusion, tissue or organ transplantation from HIV-infected donors, and cases that have more than one probable route of infection (e.g., MSM with a reported history of IDU). Infection through hemophilia/coagulation disorder was excluded from the investigation. "Risk not reported or identified" includes those with no reported history of HIV exposure, including people whose exposure history is incomplete because of death, refusal of interview, or inability to follow-up. It should be noted that, in all countries except Japan, this category also includes those cases in which the route of infection is under investigation.

Comparisons of the increasing trends at the onset of the epidemic in each country were conducted using data on AIDS cases reported in the Epidemiological Facts Sheets[21] organized by the UNAIDS/WHO (United Nations Programme on AIDS/World Health Organization) Working Group on Global HIV/AIDS and STI Surveillance. Since the onset of the epidemic, the annual trends in the number of people reported with AIDS are shown for 10 countries, including Japan, while the trends according to the route of infection are shown for 5 countries where information on exposure categories was available.

Results

Table 1 and Table 2 show the annual trends in the reported number of people with AIDS and HIV, respectively, in each country. Figure 1 shows a semi-logarithm plot of the reported cases per 1,000,000 individuals. The reported number of AIDS cases peaked in the USA and Canada in 1993, in the EU, Australia, UK, Germany, Spain, and France in 1994, and in Italy in 1995, and decreased thereafter. In contrast, the reported number in Japan continued to exponentially increase even after 1993.

Table 3 shows the cumulative number of AIDS and HIV cases according to sex and age up until 2001. In Japan, the proportion of people reported with AIDS and HIV aged 40 years or older was 64.4% and 35.0%, respectively. In other industrialized countries, these percentages were, at the most, 41.9% and 25.7%, respectively.

Table 4 shows the total number of cumulative AIDS and HIV cases according to the route of infection up until 2001. In Japan, the proportion of males infected through heterosexual contact was extremely high (42.4%) compared to other industrialized countries. The ratio of males and females who contracted HIV as a result of heterosexual contact was extremely imbalanced in Japan (8.5 : 1). The proportion of AIDS cases whose risk was not reported was extremely high (20.9%) in Japan.

Figure 2 shows the increasing trend in reported AIDS cases at the onset of the epidemic in each country. The trend in Japan was extremely slow compared to other industrialized countries. Figure 3 shows the trends according to the route of infection in the countries in which this data was available. The increasing trend was again slow in Japan. There were apparent differences in the reported cases infected through MSM (including bisexual contact) and IDU.

Discussion

Analysis of surveillance data

This study was based on the reported number of people with HIV and AIDS obtained from annual reports of HIV/AIDS surveillance and Epidemiological Fact Sheets from each country. The problems that must be considered in the analysis of the surveillance data are the completeness of coverage, reporting delays, and duplicate reports.

The coverage rate of AIDS cases will be high because AIDS cases have specific symptoms and tend to make more use of medical facilities. In Japan, the reported rate of AIDS diagnosis in the HIV/AIDS surveillance was more than 90%[22]. This rate was about 85% in the USA[1], 95% in

Canada[3], 90% in Australia[4], 80% in the UK[16] and 85% in Germany[17]. On the other hand, HIV infection data should be interpreted more cautiously. HIV surveillance reports might not be representative of all individuals infected with HIV, because most HIV-infected individuals have no specific symptoms for a long time after HIV transmission, and not all infected individuals have been tested, hence identified. Particular care should be taken when interpreting the annual trends in reported HIV cases (Table 2 and Figure 1 (b)).

Reporting delays refer to the time between diagnosis of HIV infection or AIDS and the reporting of those events to the surveillance system. Reporting delays might vary according to exposure, geography, age, and sex, and might constitute several years for some AIDS cases. In Japan, about 95% of Japanese HIV cases and 85% of Japanese AIDS cases were reported to the surveillance system within 1 year of diagnosis[11]. In the USA, the proportions were about 93% and 88%, respectively[1], while overall in the EU about 90% of the diagnosed AIDS cases were reported within 1 year[2]. Considering the effects of these reporting delays, recent trends in the number of reported AIDS cases should be assessed by analyzing the data according to the year of diagnosis rather than the year when reported. In this study, the analyses were performed based on the year of diagnosis, except in a few countries in which the year when reported was used. However, the effect of using the year when reported on the recent

Table 1 Annual trends in the number of people reported with AIDS by country and sex.

Country	Sex	Calendar year of diagnosis																	Total
		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	
Japan[a]	Male	5	3	6	9	15	18	24	36	53	91	108	156	170	158	212	239	221	1,524
	Female	0	0	3	2	2	3	0	1	5	9	11	15	12	10	12	21	24	130
Total		5	3	9	11	17	21	24	37	58	100	119	171	182	168	224	260	245	1,654
USA		23,205[b]	19,404	29,105	36,126	43,499	49,546	60,573	79,657	79,879	73,086	69,984	61,124	49,379	41,829	38,811	36,087	24,855	816,149
EU[c]		—	—	—	—	—	—	—	21,380	23,256	26,605	25,980	22,769	16,036	12,853	11,788	11,075	9,890	255,621[d]
Canada	Male				7,273[f]				1,604	1,634	1,595	1,451	939	597	517	376	349	184	16,519
	Female				471[f]				120	125	149	141	137	107	95	76	45	35	1,501
Total[e]		646[b]	628	950	1,162	1,377	1,430	1,551	1,724	1,759	1,745	1,593	1,076	705	612	453	394	221	18,026
Australia	Male					4,065[g]				799	905	771	636	350	296	166	214	127	8,329
	Female					152[g]				46	49	38	33	31	19	20	22	17	427
Total						4,217[g]				845	954	809	669	381	315	186	236	144	8,756
UK	Male	391[b]	461	659	870	1,016	1,147	1,250	1,404	1,549	1,628	1,485	1,162	852	585	548	546	417	15,970
	Female	17[b]	13	22	38	66	97	138	173	237	225	281	268	216	190	185	234	200	2,600
Total		408[b]	474	681	908	1,082	1,244	1,388	1,577	1,786	1,853	1,766	1,430	1,068	775	733	780	617	18,570
Germany	Male	453[b]	525	964	1,163	1,448	1,386	1,578	1,656	1,711	1,796	1,610	1,320	807	689	576	502	339	18,523
	Female	23[b]	46	69	104	128	157	183	230	262	256	260	250	203	145	145	101	104	2,666
Total		476[b]	571	1,033	1,267	1,576	1,543	1,761	1,886	1,973	2,052	1,870	1,570	1,010	834	721	603	443	21,189
Italy		244[b]	458	1,030	1,775	2,482	3,134	3,827	4,261	4,814	5,524	5,662	5,051	3,370	2,418	2,111	1,876	1,296	49,333
Spain	Male	222[b]	403	897	1,868	2,635	3,221	3,720	4,101	4,423	5,904	5,655	5,201	3,758	2,746	2,299	1,966	1,590	50,680[h]
	Female	24[b]	92	192	401	522	693	839	958	1,047	1,450	1,424	1,368	982	752	595	578	390	12,322[h]
Total		246[b]	495	1,089	2,269	3,157	3,914	4,559	5,059	5,470	7,354	7,079	6,569	4,740	3,498	2,894	2,544	1,980	63,002[e]
France	Male				17,174[f]				4,305	4,418	4,601	4,202	3,185	1,774	1,488	1,360	1,218	1,009	44,734
	Female				3,136[f]				887	1,103	1,161	1,089	824	493	430	430	456	361	10,370
Total					20,310[f]				5,192	5,521	5,762	5,291	4,009	2,267	1,918	1,790	1,674	1,370	55,104

[a] Calendar year is year of report. [b] Cumulative reported numbers until the end of 1985. [c] Reported numbers in each year was adjusted for reporting delay.

[d] Cumulative total since the beginning of reporting (not adjusted for reporting delay). [e] Includes 6 persons whose sex is unknown.

[f] Cumulative reported numbers until the end of 1991. [g] Cumulative reported numbers until the end of 1992.

[h] Includes 86 persons (male 71, female 15) whose year of diagnosis is unknown.

Table 2 Annual trends in the number of people reported with HIV by country and sex.

Country	Sex	Calendar year of diagnosis																	Total
		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	
Japan[a]	Male	0	0	34	15	35	27	52	108	102	134	147	189	234	261	379	336	475	2,528
	Female	0	0	11	4	18	10	17	16	22	32	19	41	34	36	45	32	50	387
Total		0	0	45	19	53	37	69	124	124	166	166	230	268	297	424	368	525	2,915
USA[b]								—	—	—	—	—	—	—	19,393	21,419	22,144	35,575	174,026[c]
EU[d]		—	—	—	—	—	—	—	—	9,617	9,931	11,665	17,705	24,748	24,397	36,578	82,316	112,210	403,359[c]
Canada	Male						27,771[f]						1,988	1,785	1,746	1,653	1,557	1,601	38,101
	Female						3,342[f]						541	457	499	543	494	535	6,411
Total[e]							36,075[f]						2,785	2,541	2,328	2,239	2,119	2,172	50,259
Australia	Male				13,060[g]					997	921	854	838	729	661	649	664	680	20,053
	Female				893[g]					81	94	76	77	86	99	76	82	97	1,661
Total					13,953[g]					1,078	1,015	930	915	815	760	725	746	777	21,725[h]
UK[i]	Male	7,085[k]		2,199	1,719	1,866	2,169	2,269	2,201	2,084	2,039	2,070	2,100	2,063	2,052	2,113	2,420	2,685	39,134
	Female	513[k]		302	231	270	369	446	539	529	532	568	584	658	746	926	1,352	1,733	10,298
Total[j]		7,613[k]		2,509	1,952	2,140	2,543	2,715	2,741	2,614	2,571	2,640	2,684	2,723	2,799	3,042	3,772	4,419	49,477
Germany[l]										2,417	2,334	2,277	1,907	2,096	1,959	1,769	1,712	1,482	17,953

[a] Calendar year is year of report.

[b] Before 1991, surveillance of HIV infection was not standardized. The numbers of reported areas is 33, 34, 36, and 39 in calendar year order.

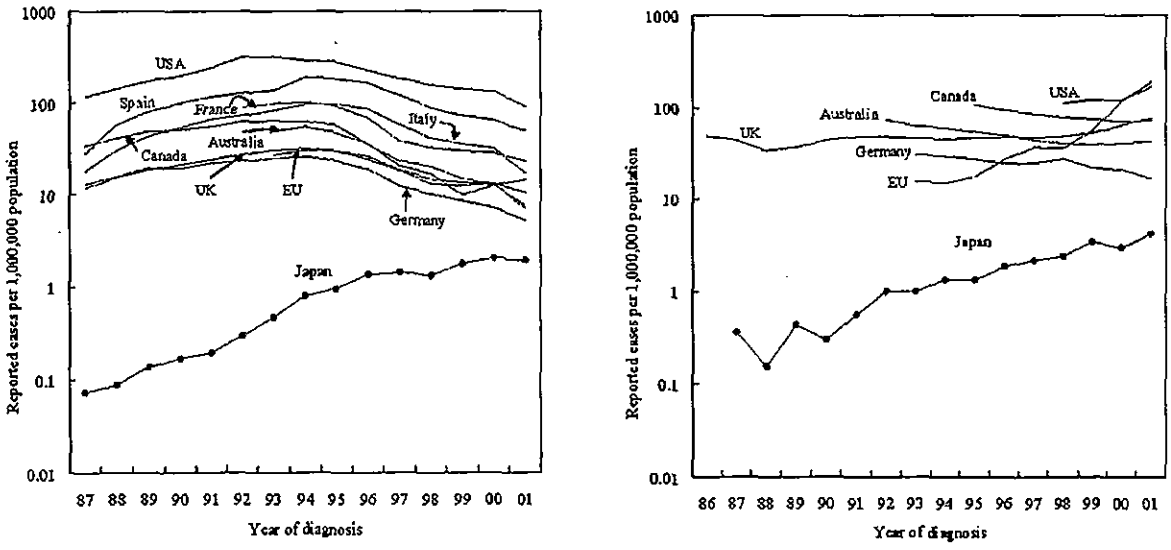
[c] *Cumulative total since the beginning of reporting* which includes persons whose year of report is unknown.

[d] Calendar year is year of report. Individual data on all cases are reported since 1997 according to a standard data file.

[e] Includes 5,747 persons whose sex is unknown. [f] Cumulative reported number until the end of 1995. [g] Cumulative reported number until the end of 1992.

[h] Includes 11 persons whose year of diagnosis is unknown. [i] Includes AIDS or death cases without the report of HIV infection.

[j] Includes 45 persons whose sex is unknown. [k] Cumulative reported number until the end of 1986. [l] Reporting is started from 1993.



(a) AIDS cases (b) HIV-infected cases

Figure 1 Annual trend in the reported number of people with (a) AIDS and (b) HIV per 1,000,000 individuals (the vertical axis is a common logarithm scale).

trend in the reported numbers of AIDS cases would be small.

Duplicate positive HIV test reports (repeated testing of the same HIV-positive individual) results in an overestimation of the number of positive reports. In Japan, if new AIDS cases that have already been reported as HIV-positive in the first HIV infection report visit different hospitals, the physicians are likely to mistake such AIDS cases for first report cases and will file the First Report. The removal of duplicates or linking the First and Second reports is difficult because of the anonymous nature of the HIV/AIDS reports in Japan. In contrast, all other countries[1-4,16-20] with HIV/AIDS surveillance systems include an identification number or code name such as the first two letters of the family name and the given name. Using such information along with the date of birth and sex data allow the detection and elimination of possible duplicate reports. This is therefore one of the defects in the HIV/AIDS surveillance system in Japan. In the future, if certain individual information is included in the surveillance data, it will be possible to exclude duplicate reports.

Differences in the hierarchy of exposure categories between countries

In all countries, HIV-infected and AIDS cases were counted only once in a hierarchy of exposure categories for surveillance purposes. This hierarchy varied slightly between countries. In this study, exposure was divided into six categories, excluding infection through hemophilia/coagulation disorders. In some countries, however, infection through "MSM+IDU" was included in the "IDU" category and infection through hemophilia/coagulation disorders was included in the "others" category. However, it is unlikely that these differences significantly change the comparative results in Table 4.

Table 3 AIDS cases and HIV infection cases by sex or age reported through the end of 2001.

HIV/AIDS	Country	Cumulative total	Sex (%)		Age (%)							
			Male	Female	-14	15-19	20-29	30-39	40-49	50-59	60-	Unknown
AIDS	Japan	1,654	92.1	7.9	0.7	0.1	10.1	24.7	31.4	23.6	9.4	0.0
	USA	816,149[a]	82.2	17.8	1.1	0.5	16.4	44.4	26.5	8.1	3.0	0.0
	EU	255,621[b]	80.7	19.3	3.8	0.7	23.6	44.3	17.5	10.1[c]		0.1
	Canada	18,026[d]	91.7	8.3	1.1	0.3	15.9	43.9	27.3	8.4	3.1	0.0
	Australia	8,756	95.1	4.9					—[e]			
	UK	18,570[f]	86.0	14.0	2.7	0.5	19.5	42.6	23.4	8.4	2.9	0.0
	Germany	21,189	87.4	12.6	0.7	0.5	15.5	41.6	25.4	12.9	3.6	0.0
	Italy	49,333	77.9	22.1	1.5	0.2	25.8	50.9	14.0	5.2	2.4	0.0
	Spain	63,002[g]	80.4	19.6	1.6	0.6	30.4	47.8	12.6	4.2	2.5	0.3
	France	55,104	81.2	18.8					—			
HIV	Japan	2,915	86.7	13.3	0.6	1.4	32.9	30.0	18.8	10.8	5.4	0.1
	USA	174,026[h]	70.6	29.4	2.2	3.8	30.2	38.1	18.9	5.2	1.6	0.0
	EU	403,359[i]	75.0	25.0	2.7	11.8	44.5	19.9	6.4	3.0[c]		11.7
	Canada	50,259[j]	85.6	14.4	1.4	1.3	24.6	37.8	18.3	7.4[c]		9.2
	Australia	21,725	92.3	7.7					—[k]			
	UK	49,477[l]	79.2	20.8	2.4	2.3	34.2	38.5	14.9	5.2	1.7	0.8
	Germany	17,953[m]	77.4	22.6	2.1	2.4	29.5	38.0	14.5	8.0	3.1	2.4

[a] Includes 1 person whose sex is unknown and 1 person whose age is unknown.

[b] Includes 7 persons whose sex is unknown and 265 persons whose age is unknown. [c] Proportion of people (%) aged 50 or older.

[d] Includes 6 persons whose sex is unknown and 2 persons whose age is unknown. [e] Median age is 37 for males and 33 for females.

[f] Includes 3 persons whose age is unknown. [g] Includes 174 persons whose age is unknown.

[h] Includes 9 persons whose sex is unknown. [i] Includes 44,116 persons whose sex is unknown and 47,304 persons whose age is unknown.

[j] Includes 5,747 persons whose sex is unknown and 4,631 persons whose age is unknown (two regions does not collect data on sex and age before 1998).

[k] Median age is 32 for males and 29 for females. [l] Includes 45 persons whose sex is unknown and 405 persons whose age is unknown.

[m] Includes 592 persons whose sex is unknown and 435 persons whose age is unknown.

Table 4 AIDS cases and HIV infection cases by route of infection reported through the end of 2001.

HIV/AIDS	Country	Route of infection (%)					
		Heterosexual contact Male	Heterosexual contact Female	MSM[a]/Bisexual contact	IDU[b]	Others	Risk not reported
AIDS	Japan	42.4	5.0	28.6	0.3	2.8	20.9
	USA	4.0	7.1	45.5	24.9	8.5	10.0
	EU[c,d]	10.0	7.7	31.4	38.3	6.5	6.1
	Canada	8.0	5.1	69.6	6.6	7.1	3.6
	Australia	4.0	2.5	80.3	3.2	6.5	3.5
	UK	11.3	11.0	65.0	6.3	5.2	1.2
	Germany[d,e]	4.1	4.7	63.2	15.5	4.7	7.8
	Italy	9.6	8.2	15.7	59.6	4.1	2.8
	Spain[e]	8.7	5.6	13.8	65.5	2.0	4.4
	France[d]	12.3	9.7	42.8	22.5	6.8	5.9
HIV	Japan	30.3	10.9	45.2	0.3	2.7	10.6
	USA	4.9	11.0	30.1	13.6	6.3	34.1
	EU[d]	5.8	6.5	11.2	39.5	2.6	34.4
	Canada[c,f]	2.7	2.3	31.4	8.2	4.9	50.5
	Australia	8.9[g]		65.0	3.8	4.8	17.5
	UK	12.8	17.3	54.7	7.8	3.8	3.6
	Germany[c,e]	12.5	12.9	35.0	10.5	2.4	26.7

[a] Men who have sex with men. [b] Injecting drug use.
[c] Excludes heterosexual contact cases whose sex is unknown.
[d] Infection through hemophilia/coagulation disorder is included in the "Others" category.
[e] Infection through MSM+IDU is included in the "IDU" category.
[f] One province does not collect data on the route of infection.
[g] No classification between males and females.

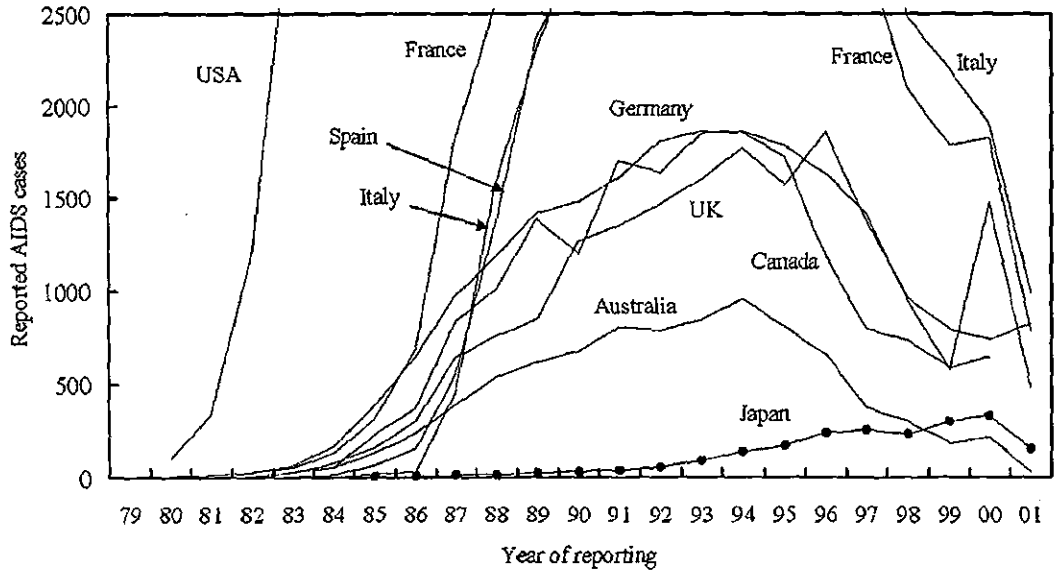
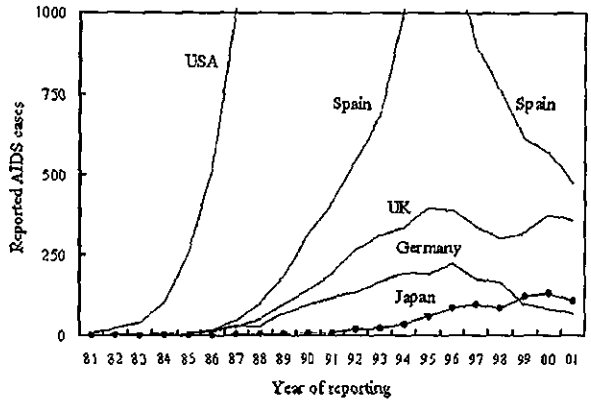
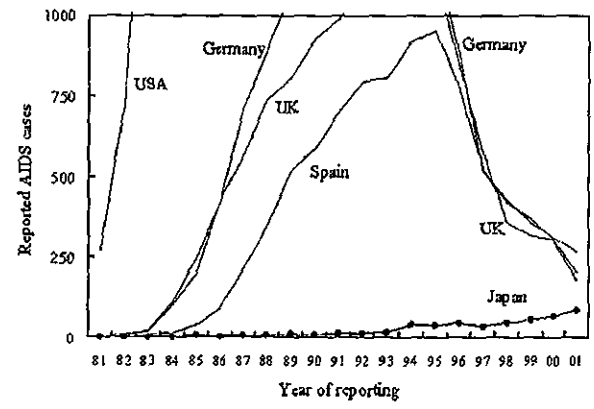


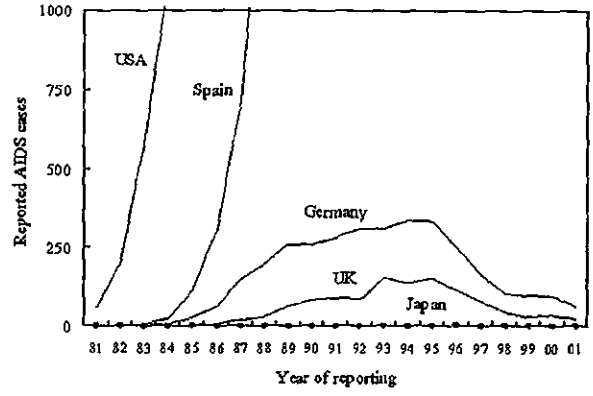
Figure 2 Increasing trends at the onset of the AIDS epidemic in each country.



(a) Heterosexual contact

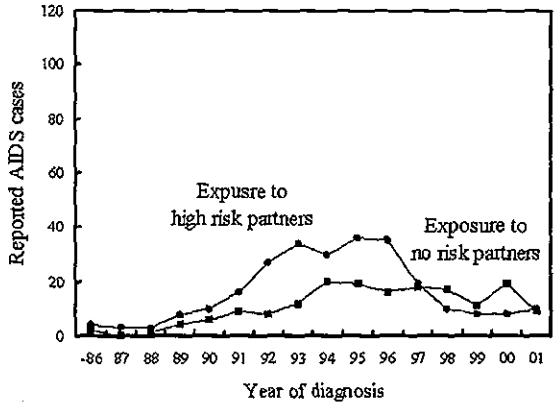


(b) MSM (men who have sex with men) /Bisexual contact

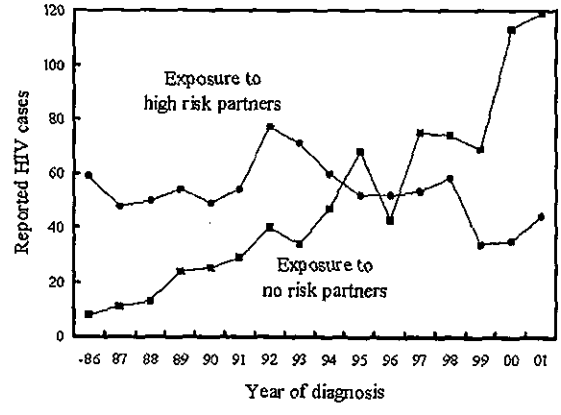


(c) IDU (injecting drug use)

Figure 3 Increasing trends at the onset of the AIDS epidemic according to the route of infection.



(a) AIDS cases



(b) HIV-infected cases

Figure 4 Annual trends in the number of women infected through heterosexual contact in the UK[16] according to the risk of partners.