Table 2 Toxicity ($n = 61$)

Toxicity	Grade 1–4	Grade 3	Grade 4
Hematological			
Leukopenia	17 (28%)	2 (3%)	0 (0)
Neutropenia	14 (23%)	0 (0%)	0 (0)
Anemia	23 (38%)	1 (2%)	2 (3%)
Thrombocytopenia	9 (15%)	2 (3%)	0 (0)
Non-hematological			
Anorexia	38 (62%)	5 (8%)	1 (2%)
Nausea	35 (57%)	2 (3%)	0 (0)
Fatigue	35 (57%)	3 (5%)	1 (2%)
Alopecia	19 (31%)	0 (0)	0 (0)
Vomiting	13 (21%)	0 (0)	0 (0)
Abdominal pain	12 (20%)	0 (0)	0 (0)
Mucositis	10 (16%)	0 (0)	0 (0)
Fever	7 (11%)	0 (0)	0 (0)
Diarrhea	5 (8%)	0 (0)	0 (0)
Transaminase elevation	4 (7%)	0 (0)	0 (0)
Rash	4 (7%)	0 (0)	0 (0)
Pigmentation	3 (5%)	0 (0)	0 (0)
Arrhythmia	2 (3%)	0 (0)	0 (0)
Taste disturbance	1 (2%)	0 (0)	0 (0)
Edema	1 (2%)	0 (0)	0 (0)
Constipation	1 (2%)	0 (0)	0 (0)
Total bilirubin	1 (2%)	0 (0)	0 (0)
Sore throat	1 (2%)	0 (0)	0 (0)
Hand–foot skin reaction	1 (2%)	0 (0)	0 (0)
BW loss	1 (2%)	0 (0)	0 (0)
DIC	1 (2%)	1 (2%)	0 (0)

BW body weight, *DIC* disseminated intravascular coagulation

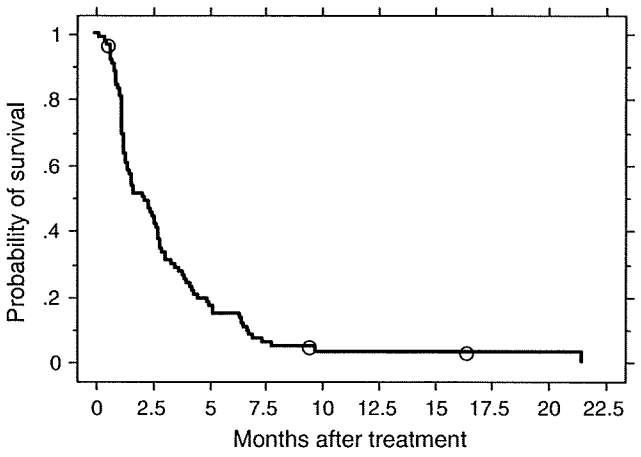

Fig. 1 Progression-free survival of all 85 patients. The median progression-free survival was 2.2 months and the 6-month survival rate was 14.3%

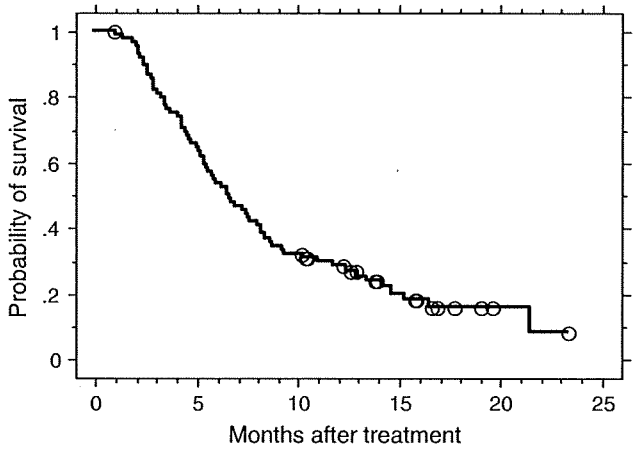

Fig. 2 Overall survival of all 85 patients. The median overall survival was 6.6 months and the 1-year survival rate was 28.2%

lesions in 3 (5.3%). Fifty of the 61 patients died: 49 patients died of cancer progression, and in the case of the other patient, the death was reported and the cause was unknown. The median PFS was 1.6 months in the 61 patients. The median OS time was 6.5 months and the 1-year survival rate was 30.0%.

Univariate and multivariate analyses

Among the 23 variables in 85 patients who received the UFD chemotherapy in the early and late phase II studies, six variables were identified as being significantly associated with shorter survival time: PS of 1, diagnosis of GBC, serum CA 19–9 level of >1,000 U/mL, T-factor of 4, serum LDH level of ≥300 IU/L, and serum total bilirubin level of ≥2.0 mg/dL by univariate analysis. The median PFS was 2.2 months in the 85 patients (Fig. 1). The median OS time was 6.6 months and the 1-year survival rate was 28.2% (Fig. 2). The median OS of patients with PS 0 was 8.2 months and that of patients with PS 1 was 4.3 months. There was a statistically significant difference in the survival curves between the two groups ($P < 0.0001$). Figure 3 shows survival curves for patients with non-GBC of ICC, ECC, or AC and for patients with GBC. The median OS of the patients with GBC was 5.4 months and that of the patients without GBC was 8.4 months. There was a statistically significant difference in the survival curves between the two groups ($P = 0.0019$). On the other hand, there was no statistically significant difference in the survival among patients with ICC, ECC, or AC.

Multivariate regression analysis was conducted for the six variables found to have prognostic significance in the univariate analysis. The four factors of PS, disease site, T-factor, and serum LDH were identified as independent prognostic factors (Table 3).

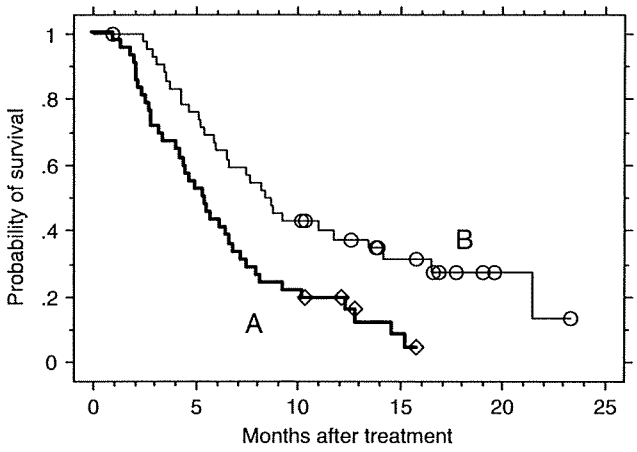

Fig. 3 Survival curves of patients with gallbladder cancer (**a**, $n = 42$) and with non-gallbladder cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or ampullary cancer (**b**, $n = 43$) ($P = 0.0019$)

Table 3 Multivariate analysis of prognostic factors in patients with unresectable biliary tract cancer

Variables	*N*	Median OS (mo)	Hazard ratio	95%CI	*P*-value
ECOG PS					
0	61	8.2	1		0.001
1	1	4.3	2.52	1.44–4.42	
Disease site					
ICC/ECC/AV	43	8.4	1		0.014
GB	42	5.4	1.88	1.14–3.12	
T-factor					
T1–3	62	8.1	1		0.035
T4	23	5.0	1.93	1.05–3.56	
LDH					
<300	67	8.1	1		0.043
≥300	18	4.8	1.85	1.02–3.35	
CA19-9					
<1,000	59	8.1	1		0.067
≥1,000	26	5.2	1.73	0.96–3.11	
T-Bil					
<2.0	77	6.6	1		0.27
>2.0	8	5.2	1.85	0.70–3.49	

OS overall survival, *CI* confidence interval, *PS* performance status, *ICC* intrahepatic cholangiocarcinoma, *ECC* extrahepatic cholangiocarcinoma, *GB* gallbladder cancer, *AV* ampullary cancer, *LDH* lactate dehydrogenase, *CA19-9* carbohydrate antigen 19-9, *T-Bil* serum total bilirubin

Discussion

Chemotherapy is generally indicated in patients with unresectable advanced cancer and patients with recurrence after resection. However, no standard chemotherapy for biliary tract cancer has yet been established, because only few randomized controlled trials with large numbers of patients have been conducted till date. Since only UFT and doxorubicin had been approved for biliary tract cancer for more than 20 years in Japan, the efficacy and safety of combinations of UFT and doxorubicin were examined in two phase II studies. The expected response rate was set as 15%, because biliary tract cancer was considered to be chemoresistant. The overall response rate in the two phase II studies was 8.7% (95% CI, 2.6–14.7%). The upper limit of the 95% confidence interval did not reach 15%, and the combination of UFT and doxorubicin was decided to have minimum activity against biliary tract cancer.

Response rate is sometimes not correlated with OS. Eckel et al. reported a pooled analysis of clinical trials in biliary tract cancer [28]. Based on the analysis of 104 phase II studies comprising of 112 trial arms, there was a highly significant correlation between time to progression (TTP) and OS ($r = 0.73$, $P = 0.000$), but there was a significant weak correlation between response rate and OS ($r = 0.2$, $P = 0.043$). Furthermore, it was reported that the pooled tumor control rate was 57.3% (95% CI: 55.3–59.3%), the median TTP was 4.1 months, and the median OS was 8.2 months. In the current studies, the tumor control rate (CR + PR + SD) was 56.4% (95% CI: 44.1–66.1%), which was almost equal to the pooled TCR, but the median PFS and OS were inferior to those of the pooled analysis, only 2.2 months and 6.6 months, respectively. The TTP or PFS seems appropriate as a surrogate marker of OS compared to the TCR.

It is difficult to conduct clinical trials consisting of a large number of patients with biliary tract cancer, because complications such as obstructive jaundice or cholangitis make it difficult to recruit eligible patients. Therefore, most of the clinical trials of chemotherapy for biliary tract cancer consist of less than 50 patients. Owing to the lack of clinical trials with large patient numbers, few analyses of prognostic factors in patients with advanced biliary tract cancer who received chemotherapy have been conducted till date. In the current phase II studies, 85 patients who received the same regimen of chemotherapy were enrolled and the patient characteristics in the two studies were almost the same. Therefore, we tried to determine the prognostic factors with univariate and multivariate analyses. Although some limitations of these methods should be recognized, such as insufficient patient number to allow adequate statistical power to be obtained, four factors, namely, the PS, disease site, T-factor, and serum LDH were identified as independent prognostic factors; PS was the most important prognostic factor with a hazard ratio of 2.52 ($P = 0.001$).

It has been reported for the advanced stage of various cancers, including pancreatic cancer, that the survival differs significantly depending on the extent of disease, that

is, depending on whether the disease is locally advanced or metastatic. In the current study, the median OS of the patients with locally advanced cancer was longer than that of patients with metastatic disease (8.2 months vs. 5.8 months), although there was no statistically significant difference in survival between the two patient groups ($P = 0.18$). We believe that this could possibly be explained by the smaller number of patients with locally advanced disease ($n = 15$) compared to that with metastatic disease ($n = 70$).

Performance status is often mentioned as an important independent prognostic factor in various cancers such as pancreatic cancer and hepatocellular carcinoma. The clinical practice guideline for the management of biliary tract cancer in Japan recommends that patients with a PS of two or more should not receive chemotherapy at the present time [29]. Since most clinical trials of chemotherapy for biliary tract cancer conducted till date have included patients with a PS of 2, the protocol of the current study also allowed the entry of patients with a PS of 2. However, only patients with a PS of 0 or 1 were actually enrolled. We investigated the prognostic factors to distinguish between PS 0 and 1, and found a statistically significant difference in survival between PS 0 and 1. The median OS in patients with a PS of 0 was 8.2 months and in patients with a PS of 1 was 4.3 months. Patients with a PS of 1 may be candidates for chemotherapy, but the survival is shorter than that in patients with a PS of 0.

The heterogeneity of biliary tract cancer is recognized to be one of the most important issues in considering prognosis of patients with biliary tract cancer. Regarding the primary site, the median OS in patients with gallbladder cancer was statistically significantly shorter than that in patients with intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma or ampullary cancer in the current study ($P = 0.014$). Some other trials showed this tendency [16, 20] but some did not [11, 12, 26]. The reason for this discrepancy is not clear but the small number of patients in each trial may be one of the reasons. In a retrospective analysis of a large number of patients ($n = 179$) [30], the median OS was 8.44 months for intrahepatic cholangiocarcinoma, 10.15 months for extrahepatic cholangiocarcinoma, and 6.50 months for gallbladder cancer. There was a statistically significant difference between extrahepatic cholangiocarcinoma and gallbladder cancer ($P = 0.029$). In the current study, a multivariate analysis in patients with unresectable biliary tract cancer who received the same regimen revealed that the site of disease was one of the significant prognostic factors. Therefore, PS and tumor site of gallbladder cancer or non-gallbladder cancer should be considered in randomized clinical trials for unresectable biliary tract cancer.

No standard chemotherapy for biliary tract cancer has yet been established till date. In Japan, recently, two registration phase II studies of a single agent, gemcitabine and S-1, have been reported [13, 26]. Gemcitabine achieved a better response rate, PFS, and OS compared with the UFT or UFD regimens. Furthermore, S-1 also seems active. Both gemcitabine and S-1 were well tolerated. Based on these results, gemcitabine and S-1 were approved for the treatment of biliary tract cancer in June 2006 and August 2007, respectively.

In conclusion, combination chemotherapy with UFT and doxorubicin (the UFD regimen) was well tolerated but showed minimum activity against advanced biliary tract cancer. Further studies of gemcitabine, S-1, and other cytotoxic or molecular targeted agents are expected to lead to the establishment of a standard chemotherapy for biliary tract cancer.

Acknowledgments This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour, and Welfare of Japan.

References

1. Sobin LH, Wittekind CH (eds) (2002) TNM classification of malignant tumours. Liver, UICC, 6th edn. Wiley-Liss, New York, pp 82–83
2. National Cancer Center. Cancer statistics in Japan 2007. http://www.fpcr.or.jp/publication/statistics.html. Accessed 10 March, 2008
3. Glimelius B, Hoffman K, Sjoden PO et al (1996) Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 7:593–600
4. Hejna M, Pruckmayer M, Raderer M (1998) The role of chemotherapy and radiation in the management of biliary cancer: a review of the literature. Eur J Cancer 34:977–986
5. Falkson G, MacIntyre JM, Moertel CG (1984) Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. Cancer 54:965–969
6. Patt YZ, Jones DV Jr, Hoque A, Lozano R, Markowitz A, Raijman I et al (1996) Phase II trial of intravenous fluorouracil and subcutaneous interferon alpha-2b for biliary tract cancer. J Clin Oncol 14:2311–2315
7. Harvey JH, Smith FP, Schein PS (1984) 5-Fluorouracil, mitomycin, and doxorubicin (FAM) in carcinoma of the biliary tract. J Clin Oncol 2:1245–1248
8. Ellis PA, Norman A, Hill A et al (1995) Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 31A:1594–1598
9. Morizane C, Okada S, Okusaka T, Ueno H, Saisho T (2003) Phase II study of cisplatin, epirubicin, and continuous-infusion 5-fluorouracil for advanced biliary tract cancer. Oncology 64:475–476
10. Rao S, Cunningham D, Hawkins RE et al (2005) Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. Br J Cancer 92:1650–1654
11. Penz M, Kornek GV, Raderer M et al (2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 12:183–186

12. Tsavaris N, Kosmas C, Gouveris P et al (2004) Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. Invest New Drugs 22:193–198
13. Okusaka T, Ishii H, Funakoshi A et al (2006) Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 57:647–653
14. Hsu C, Shen YC, Yang CH et al (2004) Weekly gemcitabine plus 24-h infusion of high-dose 5-fluorouracil/leucovorin for locally advanced or metastatic carcinoma of the biliary tract. Br J Cancer 90:1715–1719
15. Alberts SR, Al-Khatib H, Mahoney MR et al (2005) Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. Cancer 103:111–118
16. Knox JJ, Hedley D, Oza A et al (2005) Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 23:2332–2338
17. Cho JY, Paik YH, Chang YS et al (2005) Capecitabine combined with gemcitabine (CapGem) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. Cancer 104:2753–2758
18. Doval DC, Sekhon JS, Gupta SK et al (2004) A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. Br J Cancer 90:1516–1520
19. Thongprasert S, Napapan S, Charoentum C et al (2005) Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. Ann Oncol 16:279–281
20. Andre T, Tournigand C, Rosmorduc O et al (2004) Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 15:1339–1343
21. Kuhn R, Hribaschek A, Eichelmann K et al (2002) Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas. Invest New Drugs 20:351–356
22. McWilliams RR, Foster NR, Quevedo FJ et al (2007) NCCTG phase I/II trial (N9943) of gemcitabine and pemetrexed in patients with biliary tract or gallbladder carcinoma: phase II results. J Clin Oncol, Proc Am Soc Clin Oncol 25:217s (abstr 4578)
23. Fujii S, Ikenaka K, Fukushima M, Shirasaka T (1978) Effect of uracil and its derivatives on antitumor activity of 5-fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil. Jpn J Cancer Res (Gann) 69:763–772
24. Pazdur R, Lassere Y, Diaz-Canton E, Bready B, Ho DH (1996) Phase I trials of uracil-tegafur (UFT) using 5 and 28 day administration schedules: demonstration of schedule-dependent toxicities. Anticancer Drugs 7:728–733
25. Furuse J, Okusaka T, Funakoshi A, Yamao K, Nagase M, Ishii H et al (2006) Early phase II study of uracil-tegafur plus doxorubicin in patients with unresectable advanced biliary tract cancer. Jpn J Clin Oncol 36:552–556
26. Furuse J, Okusaka T, Boku N, Ohkawa S, Sawaki A, Masumoto T, Funakoshi A (2008) S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: a multicenter phase II study. Cancer Chemother Pharmacol 62(5):849–855
27. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
28. Eckel F, Schmid RM (2007) Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 96:896–902
29. Furuse J, Takada T, Miyazaki M et al (2008) Guidelines for chemotherapy of biliary tract and ampullary carcinomas. J Hepatobiliary Pancreat Surg 15:55–62
30. Yonemoto N, Furuse J, Okusaka T, Yamao K, Funakoshi A, Ohkawa S, Boku N, Tanaka K, Nagase M, Saisho H, Sato T (2007) A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. Jpn J Clin Oncol 37:843–851

CHEST

Original Research

RESPIRATORY INFECTION

Health-Care–Associated Pneumonia Among Hospitalized Patients in a Japanese Community Hospital*

Yuichiro Shindo, MD; Shinji Sato, MD, PhD; Eiichi Maruyama, MD; Takamasa Ohashi, MD, PhD; Masahiro Ogawa, MD; Naozumi Hashimoto, MD, PhD; Kazuyoshi Imaizumi, MD, PhD; Tosiya Sato, PhD; and Yoshinori Hasegawa, MD, PhD, FCCP

Background: **Health-care–associated pneumonia (HCAP) is a relatively new concept. Epidemiologic studies are limited, and initial empirical antibiotic treatment is still under discussion. This study aimed to reveal the differences in mortality and pathogens between HCAP and community-acquired pneumonia (CAP) in each severity class, and to clarify the strategy for the treatment of HCAP.**

Methods: **We conducted a retrospective observational study of patients with HCAP and CAP who were hospitalized between November 2005 and January 2007, and compared baseline characteristics, severity, pathogen distribution, antibiotic regimens, and outcomes. In each severity class (mild, moderate, and severe) assessed using the A-DROP scoring system (*ie*, age, dehydration, respiratory failure, orientation disturbance, and low BP), we investigated the in-hospital mortality and occurrence of potentially drug-resistant (PDR) pathogens.**

Results: **A total of 371 patients (141 HCAP patients, 230 CAP patients) were evaluated. The proportion of patients in the severe class was higher in the HCAP patients than in CAP patients. In the moderate class, the in-hospital mortality proportion of HCAP patients was significantly higher than that of CAP patients (11.1% vs 1.9%, respectively; p = 0.008). In moderate-class patients in whom pathogens were identified, PDR pathogens were isolated more frequently from HCAP patients than from CAP patients (22.2% vs 1.9%, respectively; p = 0.002). The occurrence of PDR pathogens was associated with initial treatment failure and inappropriate initial antibiotic treatment.**

Conclusions: **The present study provides additional evidence that HCAP should be distinguished from CAP, and suggests that the therapeutic strategy for HCAP in the moderate class holds the key to improving mortality. Physicians may need to consider PDR pathogens in selecting the initial empirical antibiotic treatment of HCAP.** ***(CHEST 2009; 135:633–640)***

Key words: antibiotics; drug resistance; mortality; pathogens; severity

Abbreviations: A-DROP = age, dehydration, respiratory failure, orientation disturbance, low BP; ATS = American Thoracic Society; CAP = community-acquired pneumonia; CI = confidence interval; ESBL = extended-spectrum β-lactamase; HAP = hospital-acquired pneumonia; HCAP = health-care–associated pneumonia; IDSA = Infectious Diseases Society of America; MDR = multidrug-resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; NHAP = nursing home-acquired pneumonia; PDR = potentially drug-resistant

Health-care–associated pneumonia (HCAP) is a relatively new concept and has been documented in the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines.[1] Previously, HCAP substantially overlapped community-acquired pneumonia (CAP). However, HCAP has been excluded from CAP because the epidemiologic pattern of HCAP is similar to that of hospital-acquired pneumonia (HAP).[2] Although a number of studies[3–5] regarding nursing home-acquired pneumonia (NHAP) and pneumonia in residents of long-term care facilities have been published in the past decade, those studies on HCAP, as newly defined by the 2005 ATS/IDSA guidelines,[1] are inadequate, and further evidence is required.

For the initial empirical treatment of patients with HCAP, the 2005 ATS/IDSA guidelines[1] recommended the administration of broad-spectrum antibiotics. This is the same strategy as that recommended for patients with HAP and ventilator-associated pneumonia, who had risk factors for multidrug-resistant (MDR) pathogens. However, practice guidelines[1,6–11] for NHAP have recommended a different strategy using an antibacterial regimen. The differences are encapsulated in the following questions: (1) should we follow the strategy for CAP or HAP? and (2) should we routinely consider MDR pathogens in determining the empirical treatment? The British Thoracic Society guidelines[10,12] have documented that patients with NHAP should be treated as having CAP because there is no difference in the distribution of causative pathogens between patients with NHAP and other older adults with CAP. Carratalà and Garcia-Vidal[13] reported that broad-spectrum antibiotic therapy should be administered to patients with HCAP having risk factors for resistant pathogens. Consequently, the selection of antibiotics for the initial empirical treatment of HCAP is still under discussion.

For editorial comment see page 594

The 2007 IDSA/ATS guidelines[2] for CAP recommend empirical antibiotic treatment in each severity class because of the differences in infecting pathogens. On the other hand, the 2005 ATS/IDSA guidelines[1] for HAP, ventilator-associated pneumonia, and HCAP recommend considering risk factors for MDR pathogens, not the severity of the patient's disease, in selecting empirical antibiotic agents. However, the differences in mortality and infecting pathogens in each severity class among patients with HCAP have not been clearly demonstrated in previous studies.[14–16] We consider that a description of mortality and infecting pathogens in each severity class would be useful as a means of outlining the differences between HCAP and CAP. The objective of this study was to determine the differences in baseline characteristics, mortality, and pathogens between HCAP and CAP patients, and to clarify the strategy for the treatment of HCAP. In particular, we focused on in-hospital mortality and identified pathogens in each severity class.

*From the Department of Respiratory Medicine (Drs. Shindo, Hashimoto, Imaizumi, and Hasegawa), Nagoya University Graduate School of Medicine, Nagoya, Japan; the Department of Respiratory Medicine (Drs. S. Sato, Maruyama, Ohashi, and Ogawa), Handa City Hospital, Aichi, Japan; and the Department of Biostatistics (Dr. T. Sato), Kyoto University School of Public Health, Kyoto, Japan.

The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Manuscript received June 8, 2008; revision accepted October 2, 2008.

Correspondence to: Yuichiro Shindo, MD, Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan; e-mail: yshindo@med.nagoya-u.ac.jp

DOI: 10.1378/chest.08-1357

Materials and Methods

Study Design and Patient Population

We conducted a retrospective observational study of patients with pneumonia hospitalized at Handa City Hospital (a 500-bed community hospital in Handa City, Aichi, Japan) between November 1, 2005, and January 31, 2007. Patients with HAP were excluded. We categorized the study patients into HCAP or CAP groups, and compared baseline characteristics, disease severity, pathogen distribution, antibiotic regimens, and outcomes between the pneumonia groups. We adhered to the Japanese ethical guidelines for epidemiologic studies, and our study protocol was approved by the Institutional Review Boards of Nagoya University Graduate School of Medicine and Handa City Hospital.

Definitions

HCAP and CAP were defined according to ATS/IDSA guidelines.[1,2] HCAP included patients with any of the following: (1) hospitalization for ≥ 2 days in the preceding 90 days; (2) residence in a nursing home or extended care facility; (3) home infusion therapy (including antibiotics); (4) long-term dialysis (including hemodialysis and peritoneal dialysis) within 30 days of entering the study; and (5) home wound care. Comorbidities were defined as described previously.[17] The outcome measures evaluated were 30-day survival or discharge from the hospital within 30 days, in-hospital mortality, initial treatment failure, and inappropriate initial antibiotic treatment. Initial treatment failure was defined as death during initial treatment or change of therapeutic agents from initial agents to others after 48 h due to clinical instability (*eg*, lack of response or worsening of fever pattern, respiratory condition, and/or radiographic status; requiring mechanical ventilation; and requiring aggressive fluid resuscitation or vasopressors). Initial antibiotic treatment was classified as being inappropriate if the initially prescribed antibiotics were not active against the identified pathogens based on *in vitro* susceptibility testing.[16] Predicted theoretical susceptibility was applied for atypical pathogens (*Mycoplasma pneumoniae*, Chlamydophila species, and Legionella species), which were considered to be fully susceptible to therapy with macrolides and fluoroquinolones.[18]

Microbiological Evaluation

Pathogens in samples obtained from respiratory tracts, blood, and other samples were investigated. These samples were cultured in sheep blood agar, chocolate agar, and potato dextrose agar in a semiquantitative manner. Positive bacterial culture results for respiratory tracts, except the normal flora, are described in the table of microbial identification. Serologic methods using single or paired sera were used to detect antibodies against *M pneumoniae* and *Chlamydophila pneumoniae*.[19,20] *Legionella pneumophila* serogroup 1 antigen in urine was detected by immunochromatography. The antibiotic sensitivity of microbes was determined using a microdilution panel (MicroScan; Dade Behring Inc; Tokyo, Japan) according to the National Committee

for Clinical Laboratory Standards guidelines.[21] The results obtained with ciprofloxacin were used to predict results for pazufloxacin because their efficacies were similar.[22]

In a previous study,[23] methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* were reported as potentially drug-resistant (PDR) bacteria. These bacteria were documented as MDR pathogens in the 2005 ATS/IDSA guidelines.[1] Moreover, it is problematic that extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (*eg*, Klebsiella species and *Escherichia coli*) have been increasing.[24] In the present study, MRSA, Pseudomonas species, Acinetobacter species, *S maltophilia*, and ESBL-producing Enterobacteriaceae were considered as PDR pathogens.

Severity Evaluation

The severity of pneumonia was evaluated using the predictive rule for CAP; that is, the A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low BP) scoring system of the 6-point scoring system proposed by the Japanese Respiratory Society, which is a modified version of the CURB-65 (*ie*, confusion, BUN > 20 mg/dL, respiratory rate ≥ 30 breaths/min, systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg, and age ≥ 65 years) clinical prediction rule and assesses the following parameters: (1) age (men, ≥ 70 years; women, ≥ 75 years); (2) dehydration (BUN concentration ≥ 21 mg/dL); (3) respiratory failure (pulse oximetric saturation ≤ 90%; PAo_2 ≤ 60 mm Hg, or Pao_2/fraction of inspired oxygen ratio ≤ 300); (4) orientation disturbance (confusion); and (5) low BP (systolic BP ≤ 90 mm Hg).[17,25,26] According to the A-DROP scores, we divided the patients into three severity classes (mild, 0; moderate, 1 or 2; and severe, 3 to 5). The predicted 30-day mortality proportion, which was reported in our recent study,[17] was categorized as follows: mild, 0%; moderate, 2.5%; and severe, 23.3%. In each severity class, we described the proportion of in-hospital mortality and occurrence of PDR pathogens for both pneumonia groups.

Statistical Analysis

A statistical software package (SPSS for Windows, version 16.0J; SPSS Inc; Chicago, IL) was used for all statistical comparisons. The α level for significance was < 0.05. Baseline characteristics, the proportion of 30-day survival or hospital discharge within 30 days, the proportion of in-hospital mortality, initial treatment failure, and the occurrence of PDR pathogens were compared between the two groups. The χ^2 test was used for analyzing discrete variables, the Wilcoxon test for continuous variables, and the trend test for an ordinal variable. In the analyses to assess the relationship between PDR pathogens and possible risk factors, and that among initial treatment failure, inappropriate initial antibiotic treatment, and PDR pathogens among HCAP patients, we calculated risk ratios and associated 95% confidence intervals (CIs).

RESULTS

Patient Characteristics

A total of 371 patients were evaluated during the study period, comprising 141 patients with HCAP (38.0%) and 230 patients with CAP (62.0%). The backgrounds of the 141 HCAP patients are shown in Table 1, and the baseline characteristics of patients with HCAP and CAP are presented in Table 2.

Table 1—*Backgrounds of 141 Patients With HCAP

Backgrounds	No. (%)
Hospitalization for ≥ 2 d in the preceding 90 d	55 (39.0)
Residence in a nursing home or extended care facility	86 (61.0)
Home infusion therapy (including antibiotics)	23 (16.3)
Long-term dialysis within 30 d	10 (7.1)
Home wound care	3 (2.1)

*Including overlapping cases.

Pathogen Distribution

The microbes identified in the HCAP and CAP groups are shown in Table 3. Laboratory cultures were obtained from the respiratory tracts of 132 of 141 HCAP patients (93.6%) and 224 of 230 CAP patients (97.4%). The number of sputum samples evaluated for infecting pathogens was 132 of 132 in the HCAP group (100%) and 220 of 224 in the CAP group (98.2%). *Streptococcus pneumoniae* and *S aureus* were the most frequently isolated pathogens in both groups. Gram-negative pathogens, streptococci other than *S pneumoniae*, *P aeruginosa*, and MRSA were isolated more frequently in HCAP patients than in CAP patients.

Antibiotic Treatment and Clinical Outcomes

Table 4 shows the initial antibiotic treatments and clinical outcomes of patients with HCAP and CAP. HCAP patients received antibiotic monotherapy as the initial treatment more frequently than CAP patients. The proportion of 30-day survival or hospital discharge within 30 days was significantly lower, while the proportion of in-hospital mortality and inappropriate initial antibiotic treatment were significantly higher among HCAP patients than among CAP patients. Although the proportion of initial treatment failure was higher among HCAP patients than among CAP patients, the difference between the two groups was not significant.

Mortality and Occurrence of PDR Pathogens According to Severity Classification

Differences in the proportion of in-hospital mortality and occurrence of PDR pathogens in each severity class, as assessed by A-DROP, are presented in Table 5. As shown in Table 2, age distribution differed between the HCAP and CAP groups. The minimum age was 15 years in patients with CAP but 53 years in patients with HCAP. Therefore, we limited our study to patients with CAP aged ≥ 53 years to reduce the effect of age distribution. As a result, 27 patients with CAP, including 1 patient with initial treatment failure, were excluded, and there was no

Table 2—*Baseline Characteristics of Patients With HCAP and CAP

Variables	HCAP Patients (n = 141)	CAP Patients (n = 230)	p Value
Male gender	78 (55.3)	145 (63.0)	0.140
Age, yr	81.3 ± 9.8	69.7 ± 16.9	< 0.001
Age ≥ 65 yr	131 (92.9)	167 (72.6)	< 0.001
Male ≥ 70 yr†	63/78 (80.8)	85/145 (58.6)	0.001
Female ≥ 75 yr†	60/63 (95.2)	42/85 (49.4)	< 0.001
Comorbidities			
Neoplastic disease	20 (14.2)	34 (14.8)	0.874
Chronic lung disease	38 (27.0)	82 (35.7)	0.082
Congestive heart failure	22 (15.6)	21 (9.1)	0.059
Chronic renal disease	14 (9.9)	5 (2.2)	0.001
Chronic liver disease	0 (0)	8 (3.5)	0.025
Central nervous system disorder	59 (41.8)	46 (20.0)	< 0.001
Diabetes	25 (17.7)	40 (17.4)	0.934
Immunosuppression	13 (9.2)	17 (7.4)	0.531
Two or more comorbidities	54 (38.3)	72 (31.3)	0.167
Clinical parameters			
Orientation disturbance (confusion)	60 (42.6)	32 (13.9)	< 0.001
Systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg	43 (30.5)	66 (28.7)	0.712
Pulse rate ≥ 125 beats/min	14 (9.9)	23 (10.0)	0.982
Respiratory rate ≥ 30 breaths/min‡	42 (32.3)	41 (20.6)	0.017
Spo_2 ≤ 90%, Pao_2 ≥ 60 mm Hg, or Pao_2/Fio_2 ≥ 300§	85 (60.3)	106 (46.1)	0.008
Laboratory findings			
BUN ≥ 21 mg/dL	69 (48.9)	73 (31.7)	0.001
pH < 7.35‖	18 (14.9)	10 (5.2)	0.003
Na < 130 mmol/L	12 (8.5)	8 (3.5)	0.037
Glucose ≥ 250 mg/dL	7 (5.0)	12 (5.2)	0.915
Hematocrit < 30%	22 (15.6)	15 (6.5)	0.005
Radiographic findings			
Bilateral lung involvement	41 (29.1)	64 (27.8)	0.795
Involvement of two or more zones¶	59 (41.8)	80 (34.8)	0.173
Pleural effusion	22 (15.6)	27 (11.7)	0.286
Use of antibiotics within the previous 90 d	89# (63.1)	48 (20.9)	< 0.001
Probable aspiration**	82 (58.2)	42 (18.3)	< 0.001
Tube feeding	14 (9.9)	1 (0.4)	< 0.001
Poor functional status††	81 (57.4)	25 (10.9)	< 0.001
A-DROP severity class			< 0.001‡‡
Mild (score, 0)	4 (2.8)	60 (26.1)	
Moderate (score, 1 or 2)	72 (51.1)	116 (50.4)	
Severe (score, 3–5)	65 (46.1)	54 (23.5)	

*Data are presented as No. (%) or mean ± SD, unless otherwise indicated. Spo_2 = pulse oximetric saturation; Fio_2 = fraction of inspired oxygen.
†Values are No. of patients/total No. of patients (%).
‡Respiratory rate was evaluated in 329 of all study patients (88.7%) on arrival at the hospital.
§One patient with Spo_2 94% and Fio_2 0.28 was included because oxygen status was not confirmed while breathing room air.
‖Arterial blood gas analysis was performed in 314 of the study patients (84.6%) on arrival at the hospital.
¶Lungs were divided artificially into six zones on the radiograph: right and left, upper, middle, and lower zones.
#Of 89 patients, 52 received broad-spectrum antibiotics, which included antipseudomonal penicillins, IV third- or fourth-generation cephalosporins, carbapenems, and fluoroquinolones, on > 2 days within the previous 90 days.
**Probable aspiration was defined as any witnessed aspiration before hospital admission or aspiration confirmed by the fluid-drinking test on hospital admission.
††Patients with poor functional status were defined as being bedridden or those who used a wheelchair and had difficulty walking.
‡‡Trend test.

in-hospital death and no occurrence of PDR pathogens among these 27 patients. In addition, we evaluated patients with identified pathogens by comparing the frequency of PDR pathogen occurrence among patients aged ≥ 53 years between the pneumonia groups.

First, 141 HCAP patients and 203 CAP patients were evaluated for in-hospital mortality according to severity classification. The in-hospital mortality proportion of HCAP patients was significantly higher than that of CAP patients, especially in the moderate class (11.1% vs 1.9%, respectively; p = 0.008). Although the observed in-hospital mortality proportion was high among patients in the severe class, there was no significant difference between the groups.

Second, 77 HCAP patients and 101 CAP patients were evaluated for the occurrence of PDR patho-

Table 3—*Microbes Identified in HCAP and CAP Patients

Microbes	HCAP Patients (n = 141)	CAP Patients (n = 230)
Gram-negative pathogens	34 (24.1)	30 (13.0)
Klebsiella species	10 (7.1)	4 (1.7)
ESBLs	0 (0)	0 (0)
Pseudomonas species	8 (5.7)	4 (1.7)
E coli	5 (3.5)	1 (0.4)
ESBLs	1 (0.7)	0 (0)
Haemophilus influenzae	4 (2.8)	17 (7.4)
Proteus mirabilis	4 (2.8)	1 (0.4)
Acinetobacter species	3 (2.1)	0 (0)
S maltophilia	0 (0)	0 (0)
Other Gram-negative bacteria	4 (2.8)	3 (1.3)
Gram-positive pathogens	44 (31.2)	72 (31.3)
S pneumoniae	19 (13.5)	44 (19.1)
S aureus	14 (9.9)	14 (6.1)
MSSA	9 (6.4)	12 (5.2)
MRSA	5 (3.5)	2 (0.9)
Streptococci other than *S pneumoniae*	10 (7.1)	12 (5.2)
Other Gram-positive bacteria	4 (2.8)	3 (1.3)
Atypical pathogens	1 (0.7)	16 (7.0)
C pneumoniae	1† (0.7)	13‖ (5.7)
M pneumoniae	0 (0)	2 (0.9)
L pneumophila	0 (0)	1 (0.4)
Nocardia species	1 (0.7)	0 (0)
No pathogen identified	64 (45.4)	121 (52.6)

*Data are presented as No. (%). MSSA = methicillin-sensitive *Staphylococcus aureus*.

†One suspected case in the HCAP group. One definitive and 12 suspected cases in the CAP group.

Table 4—*Antibiotic Treatment and Clinical Outcomes of Patients With HCAP and CAP

Therapy and Outcomes	HCAP Patients (n = 141)	CAP Patients (n = 230)	p Value
Initial antibiotic treatment			
Monotherapy	60 (42.6)	23 (10.0)	
β-Lactams	56 (39.7)	23 (10.0)	
Quinolones	3 (2.1)	0 (0)	
Other	1 (0.7)	0 (0)	
Combination therapy	81 (57.4)	207 (90.0)	
β-Lactams + quinolones	10 (7.1)	7 (3.0)	
β-Lactams + aminoglycosides	5 (3.5)	0 (0)	
β-Lactams + macrolides	29 (20.6)	186 (80.9)	
β-Lactams + clindamycin	35 (24.8)	13 (5.7)	
Other combinations	2 (1.4)	1 (0.4)	
30-d survival or hospital discharge within 30 d†	119 (84.4)	219 (95.2)	< 0.001
In-hospital mortality	30 (21.3)	17 (7.4)	< 0.001
Initial treatment failure	35 (24.8)	41 (17.8)	0.105
Inappropriate initial antibiotic treatment	15/72‡ (20.8)	10/103‡ (9.7)	0.038

*Values are given as No. (%), unless otherwise indicated.

†We calculated the proportion of hospital discharge within 30 days instead of the 30-day survival in patients who had no medical records indicating that they had died and were discharged from the hospital with improvement of signs and symptoms.

‡Among patients in whom pathogens were identified, we could not evaluate the appropriateness of antibiotic treatment in five patients with HCAP and four patients with CAP.

gens. In the severe class, there was no significant difference in the occurrence of PDR pathogens between HCAP and CAP patients. However, PDR pathogens were more frequently isolated among HCAP patients than among CAP patients in the moderate class (22.2% vs 1.9%, respectively; $p = 0.002$). The frequency of PDR pathogens was almost the same in the moderate and severe classes of HCAP patients, whereas it was dependent on the severity of pneumonia in CAP patients. The in-hospital mortality proportion among HCAP and CAP patients with PDR pathogens was 12.5% (one of eight patients) and 0% (zero of one patient), respectively, in the moderate class, and 44.4% (four of nine patients) and 40.0% (two of five patients), respectively, in the severe class.

Third, we assessed the roles of initial treatment failure and inappropriate initial antibiotic treatment. The in-hospital mortality proportion among HCAP patients with and without initial treatment failure was 62.9% (22 of 35 patients) and 7.5% (8 of 106 patients), respectively ($p < 0.001$); that among CAP patients with and without initial treatment failure was 32.5% (13 of 40 patients) and 2.5% (4 of 163 patients), respectively ($p < 0.001$). The in-hospital mortality proportion among HCAP patients with and without inappropriate initial antibiotic treatment was 33.3% (5 of 15 patients) and 17.5% (10 of 57 patients), respectively ($p = 0.180$); that among CAP patients with and without inappropriate initial antibiotic treatment was 30.0% (3 of 10 patients) and 11.4% (10 of 88 patients), respectively ($p = 0.100$). Furthermore, the proportion of initial treatment failure among HCAP patients without PDR pathogens was 16.7% (10 of 60 patients) and that for HCAP patients with PDR pathogens was 70.6% (12 of 17 patients). The proportion of inappropriate initial antibiotic treatment among HCAP patients without PDR pathogens was 5.4% (3 of 56 patients) and that for HCAP patients with PDR pathogens was 75.0% (12 of 16 patients). As described above, HCAP patients with PDR pathogens had a risk ratio

Table 5—*In-hospital Mortality and Occurrence of PDR Pathogens in Each Severity Class Assessed by A-DROP (Excluding Patients Aged < 53 yr)

Severity Class	HCAP Patients (n = 141)	CAP Patients (n = 203†)	p Value
In-hospital mortality‡			
Mild	0 (0/4)	0 (0/41)	
Moderate	11.1 (8/72)	1.9 (2/108)	0.008
Severe	33.8 (22/65)	27.8 (15/54)	0.476
Total	21.3 (30/141)	8.4 (17/203)	0.001
Occurrence of PDR pathogens§			
Mild	0 (0/0)	0 (0/15)	
Moderate	22.2 (8/36)	1.9 (1/52)	0.002
Severe	22.0 (9/41)	14.7 (5/34)	0.423
Total	22.1 (17/77)	5.9 (6/101)	0.001

*Values are given as % (No. of patients/total No. of patients), unless otherwise indicated.

†Twenty-seven patients with CAP who were < 53 years old (minimum age of patients with HCAP) were excluded to reduce the effect of age distribution.

‡Causes of death in the moderate class were as follows: among patients with HCAP, worsening of pneumonia in four patients and relapse of pneumonia in four patients; among patients with CAP, worsening of pneumonia in one patient and pancreatic cancer in another patient. Among the dead patients in whom pathogens were isolated in the moderate class, PDR pathogens were isolated in one of three patients (33.3%) with HCAP and zero of one patient with CAP. Causes of death in the severe class were as follows: among patients with HCAP, worsening of pneumonia in 17 patients and relapse of pneumonia in 5 patients; among patients with CAP, worsening of pneumonia in 7 patients, relapse of pneumonia in 6 patients, and other diseases (myocardial infarction and adult T-cell leukemia) in 2 patients. Among dead patients in whom pathogens were isolated in the severe class, PDR pathogens were isolated in 4 of 13 patients (30.8%) with HCAP and 2 of 12 patients (16.7%) with CAP.

§We evaluated patients in whom pathogens were identified; CAP patients < 53 years old were excluded. HCAP patients, n = 77; CAP patients, n = 101.

of 4.2 (95% CI, 2.2 to 8.1; $p < 0.001$) with respect to initial treatment failure and 14.0 (95% CI, 4.5 to 43.6; $p < 0.001$) with respect to inappropriate initial antibiotic treatment.

Risk Factors for Occurrence of PDR Pathogens Among HCAP Patients

Table 6 shows risk ratios of the possible risk factors for the occurrence of PDR pathogens by univariate analyses. Of these factors, the use of broad-spectrum antibiotics on > 2 days within the previous 90 days and tube feeding were significant; the corresponding risk ratios were 3.1 and 2.5.

Discussion

This retrospective study has shown differences in baseline characteristics, disease severity, identified pathogens, initial antibiotic regimens, and clinical outcomes between HCAP and CAP patients. We especially focused on differences in mortality and identified pathogens in each severity class between HCAP and CAP patients. We found significant differences in the in-hospital mortality and occurrence of PDR pathogens in the moderate class between HCAP and CAP patients, but not in the severe class.

Previously, a substantial number of HCAP patients were defined as having CAP.[2] In order to determine the differences between HCAP and CAP patients, we evaluated the severity of HCAP using the A-DROP scoring system, which has been found to be useful in assessing the severity of CAP.[17]

We found no significant difference between HCAP and CAP patients in the in-hospital mortality and occurrence of PDR pathogens in the severe class. In contrast, in the moderate class the in-hospital mortality proportion of HCAP patients was significantly higher than that of CAP patients. These results suggest that the therapeutic strategy for the moderate class holds the key to improving mortality in HCAP patients.

In the moderate class, the occurrence of PDR pathogens among HCAP patients was significantly higher than that among CAP patients. Although an association between the occurrence of PDR pathogens and the in-hospital mortality was not found in the present study, the in-hospital mortality proportion among HCAP patients with initial treatment failure was markedly higher than that among CAP patients. Our findings suggest that the initial treatment failure among HCAP patients was more fatal than that among CAP patients, and they indicate that physicians should pay careful attention to the initial treatment of HCAP.

Micek et al[16] alerted physicians to the greater likelihood of HCAP patients receiving inappropriate initial antibiotic treatment and their greater risk of in-hospital mortality. Kollef et al[27] reported that inadequate antimicrobial treatment of infection was the most important independent determinant of hospital mortality. In addition, Craven[28] and Zilberberg et al[29] emphasized that the early initiation of appropriate and adequate antibiotic therapy was important for improving the outcomes of patients with HCAP. In the present study, HCAP patients were more likely to receive β-lactam monotherapy or β-lactams in combination with clindamycin than CAP patients. This might reflect the fact that the use of these antibiotics has been accepted in Japan for the initial empirical therapy of patients with aspiration pneumonia and NHAP.[8,9,25] As a result, HCAP patients have been receiving inappropriate initial antibiotic treatment more frequently than CAP patients. Fur-

Table 6—*Risk Factors for Occurrence of PDR Pathogens Among HCAP Patients**

Risk Factors	Yes	No	Risk Ratio	95% CI	p Value
Use of antibiotics within the previous 90 d	14/50 (28.0)	3/27 (11.1)	2.5	0.8–8.0	0.088
Use of broad-spectrum antibiotics for > 2 d within the previous 90 d†	11/31 (35.5)	5/44 (11.4)	3.1	1.2–8.1	0.012
Chronic lung disease	5/22 (22.7)	12/55 (21.8)	1.0	0.4–2.6	0.931
Probable aspiration	14/54 (25.9)	3/23 (13.0)	2.0	0.6–6.3	0.212
Tube feeding	5/11 (45.5)	12/66 (18.2)	2.5	1.1–5.7	0.044
Poor functional status	14/49 (28.6)	3/28 (10.7)	2.7	0.8–8.5	0.069
Immunosuppression	0/5 (0.0)	17/72 (23.6)			0.218

*Values are given as No. of patients/total No. of patients (%), unless otherwise indicated. We evaluated 77 patients in whom pathogens were identified.

†Broad-spectrum antibiotics comprised antipseudomonal penicillins, IV third- or fourth-generation cephalosporins, carbapenems, and fluoroquinolones. Details of the antibiotics used were not evaluated in two patients, and these patients were excluded from the study.

thermore, in-hospital death tended to occur more frequently in patients who received inappropriate initial antibiotic treatment compared with those who received appropriate initial antibiotic treatment. Therefore, HCAP should be identified as a distinct entity in determining the initial empirical antibiotic treatment, as stated in recent reports.[30,31]

In the present study, PDR pathogens occurred more frequently among HCAP patients than among CAP patients (Table 5). We found that the proportion of initial treatment failure and inappropriate initial antibiotic treatment was markedly higher among HCAP patients with PDR pathogens than among those without. More specifically, HCAP patients with PDR pathogens were 4.2 and 14.0 times as likely, respectively, to have initial treatment failure and inappropriate initial antibiotic treatment than those without PDR pathogens. Therefore, we suggest that physicians should give more consideration to PDR pathogens in choosing the initial empirical antibiotic treatment of HCAP patients to improve their management.

What population among HCAP patients should be targeted for treatment with broad-spectrum antibiotics? As shown in Table 5, the frequency of PDR pathogens was not dependent on the severity of pneumonia in HCAP patients; in this respect, these patients differed from CAP patients. In the analysis of risk factors for the occurrence of PDR pathogens (Table 6), the use of broad-spectrum antibiotics on > 2 days within the previous 90 days and tube feeding were found to be significant risk factors. Therefore, we suggest that HCAP patients with these risk factors for PDR pathogens should be treated with broad-spectrum antibiotics (an antipseudomonal β-lactam plus a fluoroquinolone or an aminoglycoside plus vancomycin or linezolid), as recommended by the 2005 ATS/IDSA guidelines,[1] even if the patients are not classified as having a severe disease.

The present study has several limitations. First, the data were retrospectively collected from a single institution. Second, the identified pathogens included oropharyngeal colonizers and were not definite causes of pneumonia since most of the results were obtained from sputum cultures; Gram staining was not performed in some cases; and the cultures were semiquantitative rather than quantitative. However, previous reports[11,32,33] have indicated a correlation between oropharyngeal colonization and pathogenesis for most episodes of NHAP or pneumonia occurring > 4 days after intubation. Third, evaluation for atypical pathogens was inadequate because of the small quantity of data.

In summary, we found that in the moderate severity class the in-hospital mortality proportion of HCAP patients was significantly higher than that of CAP patients. Moreover, in the moderate class, PDR pathogens were identified more frequently among HCAP than among CAP patients. On the other hand, in the severe class, there were no significant differences between HCAP and CAP patients in in-hospital mortality and occurrence of PDR pathogens. These results provide additional evidence that HCAP should be distinguished from CAP. Moreover, we showed that the occurrence of PDR pathogens among HCAP patients was associated with a higher proportion of initial treatment failure and inappropriate initial antibiotic treatment. We suggest that the therapeutic strategy for the moderate class holds the key to improving mortality in HCAP patients, and that physicians may need to consider PDR pathogens in choosing the initial empirical antibiotic treatment of HCAP patients in order to improve their management.

ACKNOWLEDGMENT: We thank Professor Michio Ohta (Department of Molecular Bacteriology, Nagoya University Graduate School of Medicine, Nagoya, Japan) for his comments on the microbiological evaluation.

References

1 American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171:388–416

2 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44(suppl):S27–S72

3 Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. Am J Med 1998; 105:319–330

4 Marrie TJ. Pneumonia in the long-term-care facility. Infect Control Hosp Epidemiol 2002; 23:159–164

5 Furman CD, Rayner AV, Tobin EP. Pneumonia in older residents of long-term care facilities. Am Fam Physician 2004; 70:1495–1500

6 Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society; the Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 2000; 31:383–421

7 Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37:1405–1433

8 Committee for the Japanese Respiratory Society Guidelines for the Management of Respiratory Infections. Antibacterial therapy of hospital-acquired pneumonia. Respirology 2004; 9(suppl):S16–S24

9 Committee for the Japanese Respiratory Society Guidelines for the Management of Respiratory Infections. Appendix I: nursing-home acquired pneumonia. Respirology 2004; 9(suppl):S51–S55

10 British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults: 2004 Update. Available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pneumonia/Guidelines/MACAPrevisedApr04.pdf. Accessed October 22, 2008

11 Mylotte JM. Nursing home-acquired pneumonia: update on treatment options. Drugs Aging 2006; 23:377–390

12 Lim WS, Macfarlane JT. A prospective comparison of nursing home acquired pneumonia with community acquired pneumonia. Eur Respir J 2001; 18:362–368

13 Carratalà J, Garcia-Vidal C. What is healthcare-associated pneumonia and how is it managed? Curr Opin Infect Dis 2008; 21:168–173

14 Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005; 128:3854–3862

15 Carratalà J, Mykietiuk A, Fernandez-Sabe N, et al. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. Arch Intern Med 2007; 167:1393–1399

16 Micek ST, Kollef KE, Reichley RM, et al. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother 2007; 51:3568–3573

17 Shindo Y, Sato S, Maruyama E, et al. Comparison of severity scoring systems A-DROP and CURB-65 for community-acquired pneumonia. Respirology 2008; 13:731–735

18 Roson B, Carratalà J, Fernandez-Sabe N, et al. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004; 164:502–508

19 Ishida T, Hashimoto T, Arita M, et al. Etiology of community-acquired pneumonia in hospitalized patients: a 3-year prospective study in Japan. Chest 1998; 114:1588–1593

20 Miyashita N, Ouchi K, Kawasaki K, et al. Comparison of serological tests for detection of immunoglobulin M antibodies to *Chlamydophila pneumoniae*. Respirology 2008; 13:427–431

21 National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 6th ed. Wayne, PA: National Committee for Clinical Laboratory Standards, 2003; document M7–A6; supplemental tables M100–S13 (M7)

22 Fukuoka Y, Ikeda Y, Yamashiro Y, et al. *In vitro* and *in vivo* antibacterial activities of T-3761, a new quinolone derivative. Antimicrob Agents Chemother 1993; 37:384–392

23 Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998; 157:531–539

24 Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001; 14: 933–951

25 Committee for the Japanese Respiratory Society Guidelines for the Management of Respiratory Infections. The Japanese Respiratory Society guidelines for the management of community-acquired pneumonia in adults. Respirology 2006; 11(suppl): S1–S133

26 Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58:377–382

27 Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999; 115:462–474

28 Craven DE. What is healthcare-associated pneumonia, and how should it be treated? Curr Opin Infect Dis 2006; 19:153–160

29 Zilberberg MD, Shorr AF, Micek ST, et al. Antimicrobial therapy escalation and hospital mortality among patients with HCAP: a single center experience. Available at: http://www.chestjournal.org/papbyrecent.dtl. Accessed on October 22, 2008

30 Abrahamian FM, Deblieux PM, Emerman CL, et al. Health care-associated pneumonia: identification and initial management in the ED. Am J Emerg Med 2008; 26:1–11

31 Kollef MH, Morrow LE, Baughman RP, et al. Health care-associated pneumonia (HCAP): a critical appraisal to improve identification, management, and outcomes; proceedings of the HCAP Summit. Clin Infect Dis 2008; 46(suppl):S296–S334

32 Verghese A, Berk SL. Bacterial pneumonia in the elderly. Medicine (Baltimore) 1983; 62:271–285

33 Ewig S, Torres A, El-Ebiary M, et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury: incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med 1999; 159:188–198

これからの薬剤開発と臨床試験

京都大学大学院医学研究科薬剤疫学*

川上浩司

1. 世界が期待する医療開発とヘルスケア産業

人類の健康の維持，向上と疾病の治療は，世界的に重要なテーマと認識されている．2009年4月27日に行われた米国立科学アカデミーでのオバマ大統領の演説では，政府研究開発投資を対GDP比3%以上にすること，理系・科学人材の育成支援とならんで，米国立衛生研究所(NIH)の予算増加や癌研究への投資が発表された．米国のみならず，英国においても医薬品，医療機器の開発に対して政府や企業は多くの投資をしており，その成果が期待されているところである．また，治療分野のみならず，健康の維持，ヘルスケアという価値も益々重要視されている．しかしながら，日本の医薬品・医療機器産業においては，日本の誇るすぐれた基盤技術が，牽引産業として昇華できていないということが懸念されている．イノベーション・エコシステムの乖離とも呼ばれる現象である．これは，決して基礎医学研究や医療従事者の能力や努力が欠如しているためではない．規制や制度のあり方が旧態依然としており国際的なイノベーション戦略になじまないということ，また，政策・行政研究，システム研究といった横断的な研究，提言が医療分野では不足してきたことが原因と考えられる．これらが産業の観点からだけでなく，人類の健康増進のためにも不利益となっていることは言うまでもない．

2. 医薬品開発の仕組みと現状

医薬品開発にかかる安全性や有効性の評価は，前臨床研究，非臨床試験，臨床試験といった研究開発段階，さらに承認，市販(製造販売承認)後の臨床試験や安全性監視を通じて行われている．

市販前の医薬品の開発のためには，製造や物理化学的性状(規格)の設定にかかるGood Manufacturing Practices (GMP)，主として動物における安全性や有効性の評価(非臨床試験という)にかかるGood Laboratory Practices (GLP)，そして人体を対象とした臨床研究を実施するうえでの科学的，倫理的妥当性を担保するためのGood Clinical Practices (GCP)といった国際標準の規制が存在している(図1)．イメージとしては，医薬品開発においては，GMPに則って試験物を準備し，GLPに則って非臨床試験を実施し，それらのデータをもとに臨床試験の計画(プロトコル)を作成し，行政当局の判断(臨床試験の認可)の後GCPに則って臨床試験を実施する，という流れである．臨床試験は，古典的には，試験物の安全

〒606-8501 京都市左京区吉田近衛町
E-mail: kawakami.k@at5.ecs.kyoto-u.ac.jp

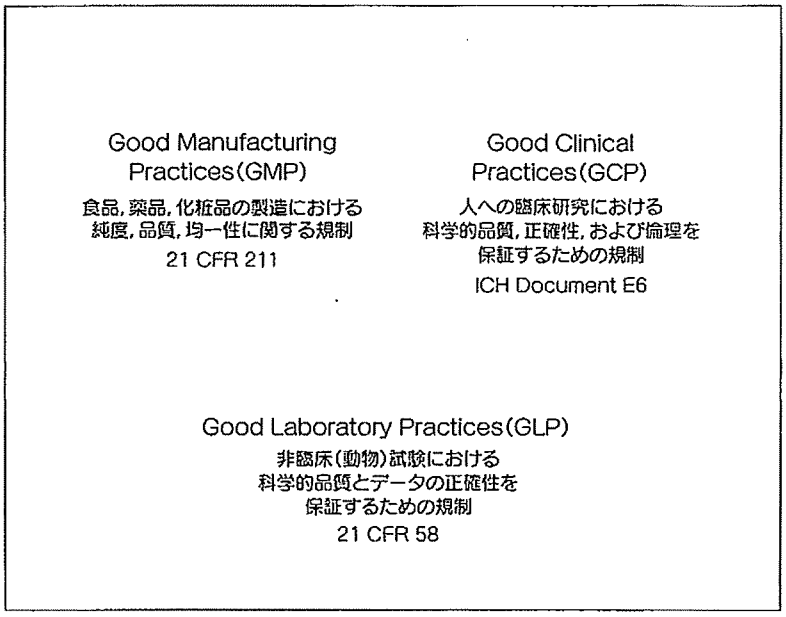

図1　医薬品の開発にかかる規制

性と忍容性，動態を評価するためのフェーズ1試験，安全性と有効性のプロファイルを評価するためのフェーズ2試験，複数の施設で同一のプロトコルに基づいて既存医薬品(あるいは偽薬)との比較を行うフェーズ3臨床試験によって構成される．なお，GCPはヘルシンキ宣言に則って臨床研究を実施するための規範だが，日本と諸外国とでは医薬品開発上の行政的位置づけは異なっている．

医薬品は開発された国々で独自に用いられるものではなく，各国で国際的に使用されるため，特に先進国(米国，欧州連合，日本)においては，各規制当局における医薬品の承認審査のためのデータ受入れの考え方，枠組みを決める組織として，医薬品規制調和国際会議(ICH；International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)が機能している．ICHが作成するガイダンスは，大きく分けて，品質(Q項；Quality)，安全性(S項；Safety)，および有効性(E項；Efficacy)からなる．日本ではICHガイドラインは厚生労働省の省令として発出されている．

米国では，臨床試験のフェーズ1，フェーズ2，フェーズ3という各段階のなかで，開発候補製剤の製造にかかる部分(米国ではcGMPと呼称する)に関しても臨床開発におけるステップに応じて向上していくことを認めるようになりつつある．すなわち，開発候補製剤の規格や製造に関する審査であるchemistry, manufacturing, and control(CMC)審査も，フェーズ1に対するcGMPは被験者の安全性を担保するために最低限の科学的妥当性をどのように評価するのかということに力点を置く，というFDA審査当局の考え方が，いわゆるフェーズ1 cGMPガイダンスとして発表された[1]．新規のバイオテクノロジー製剤のようにまだ完全に規格化や製造工程が確立できないような開発候補製剤の場合，当初は完全なGMPで製造するということは無理であっても，フェーズ3，承認申請にむけて完全なGMPを準備する，また，規格も最終的にはしっかりしたものを求めていくということになる．このように，たとえば臨床試験の入り口の部分に際して，米国では医薬品開発の時代の変革に柔軟

表1　人体への初回投与以前に必要な非臨床試験

薬理	薬物動態	毒性
薬効薬理試験	薬物動態試験	単回投与毒性試験*
安全性薬理コアバッテリー試験*	トキシコキネティクス*	反復投与毒性試験*
		遺伝毒性試験*

＊Good Laboratory Practices (GLP) の遵守が必要な試験

に対応していこうという努力がなされているわけである．

さて，試験物が投与された時に生体内でどのような分布，機序で効果を発揮するのか，かつ障害を引き起こすことなく安全に投与しうるか，またどのような副作用が生じうるかを明らかにする必要がある．これらについて，人体に投与して調べる臨床試験に対し，細胞系や動物を用いて調べる試験は非臨床試験と呼ばれる．非臨床試験は大別して表1のような3種に分類される[2]．特に安全性薬理や毒性にかかる部分は重要であるため，大学など研究機関ではなく，GLP認証を受けている施設で実施する必要がある．また，開発対象である医薬品の候補物質の性状，期待される効果や有害作用によって，実際に実施される試験の種類の組み合わせは異なる．非臨床試験には，臨床試験を開始するにあたって，人体への投与が行われる以前に実施される必要があるもの，人体への投与が開始された後に，臨床試験の規模や投与期間が長くなるなど開発段階に応じ追加で実施されるものがある[3]．なお，バイオテクノロジー応用医薬品（生物製剤）では，その多様な構造や種特異性，多面的な生物活性を発現する可能性から，従来の毒性試験が適切でない場合がある．そのため，別途，バイオテクノロジー応用医薬品の非臨床における安全性評価に関するガイドラインが定められている[4]．

3．21世紀の薬剤開発

20世紀末になると，分子生物学の進歩により，遺伝子組み換え，培養技術を駆使した遺伝子や人工タンパクの産生が可能となった．また，ヒューマンゲノムプロジェクトの完了によって，人の臓器や体内の調節に関連した遺伝子が明らかになった．そこで，疾患に対応した遺伝子検索が可能となり，特定の遺伝子やタンパクを標的とした医薬品，すなわち分子標的医薬や抗体医薬（新世代の生物製剤）といった新世代の医薬品が創出されるようになった．この10年間で，癌治療の分野においては，抗体医薬は実に全世界の抗癌剤の売り上げの半分を占めるようにまでに成長している．ただし，抗体医薬はコストが高価なため，世界的な医療費抑制の要請と代替法の探索から，今後は市場が減少していくことが予想されている．そこで，いわゆる「ポスト抗体医薬」をどのような剤形の医薬品（あるいは生物製剤）が引き継いで，医療現場で標準的に使用されるようになるかが今後の医薬品開発の鍵となっていくであろう．

その一方で，1990年代末から，新規

有効成分が臨床試験を経て承認される確率は1万分の1ぐらいまで下がっているといわれる．1980年代半ばには米国でフェーズ1に入ったもののうちフェーズ3を終了して承認申請に入るものは20～30％であったが，現在は年間1,000本FDAに申請される臨床試験のなかで，フェーズ3を終了する画期的な新規有効成分は一桁である．このように，医薬品開発のチャンスは非常に低くなっているのである．

では，なぜ医薬品開発が困難になってきたのだろうか．治療に資する低分子化合物はもう出尽くした，という意見もあるが，上述のようなバイオテクノロジー技術の革新にともなって，新しい製剤の安全性と有効性の評価（レギュラトリーサイエンス）はまだ発展途上であるという側面があることも否めない．すなわち，タンパク製剤，核酸医薬，抗体医薬，遺伝子治療，細胞治療，組織工学利用製品といった多様な剤形について，前臨床研究段階，動物を対象として行われる安全性薬理試験などの非臨床試験，そして人を対象とした臨床試験，承認後の市販後臨床試験や市販後安全性監視と，各段階で新しい評価方法を考案，妥当性の確認をしていく必要があり，そのハードルの高さや方法論が確立していないという点も，現在の医薬品開発を困難にしている一因であると考えることができる[5]．

4．臨床試験の制度の問題点と今後

米国においては，FDAが医薬品行政の拠りどころとするInvestigational New Drug（IND）制度においては，未承認薬および生物製剤を用いた臨床試験を行う際には，その申請元（スポンサー）が大学，研究機関，バイオベンチャー，製薬企業といった形態にかかわらず，FDAに全例申請をし，科学的審査と臨床試験開始の認可を受ける必要がある．臨床試験の開始が許可されてフェーズ1，2，3と進行し，最終的に承認申請が行われる段階に至るまで，行政側はスポンサー側に対して行政側の科学者として積極的にアドバイスを行い，両者が二人三脚で医薬品開発を行っているという特徴があるといえよう．

現在，日本では，原則として薬事法の規定内での「治験」（基本的に企業が主体）という枠組みで人を対象とした臨床試験を行う場合には，独立行政法人医薬品医療機器総合機構（以下，医薬品機構）での審査・認可を経ることになっている．数年前の薬事法改正で，企業のみならず大学病院などの医療機関が医師主導型治験として医薬品機構に届出と審査を求めることもできるようになった．しかしながら，未承

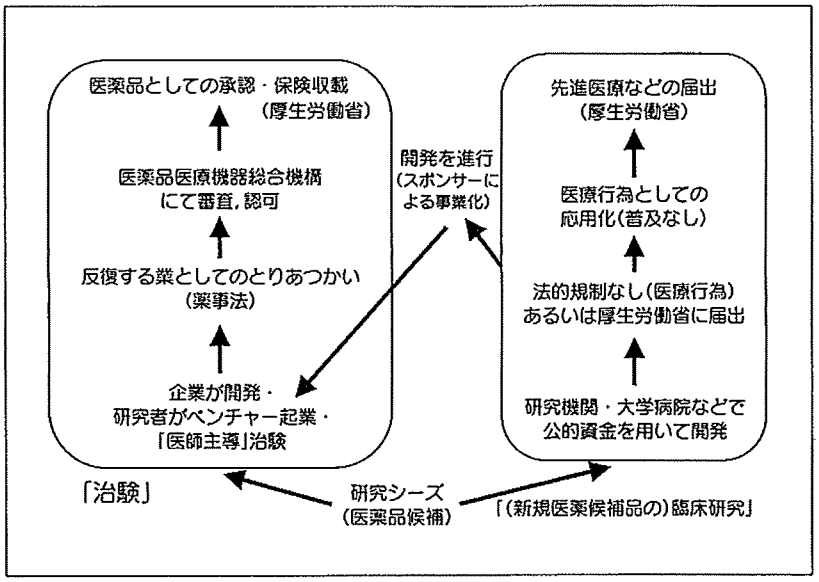

図2　我が国における臨床試験制度の現状

認の新規有効成分であっても，薬事法外の医療行為として大学などが「臨床研究」として実施する場合には，遺伝子・細胞治療品目以外は行政への届出や審査は受けない(図2)．医薬品機構での審査・認可を受けて開発を進める場合は，臨床試験(治験)が終了し，厚生労働省からの承認が得られると，最終的には薬価収載となり，国内の医療機関での当該医薬品の使用が可能となる．一方，「臨床研究」として，治験ではなく開発を行った場合のゴールは，先進医療のように当該医療施設だけで国からの医療費が受けられるというものになる(特定療養費制度)．動物や人由来の組織や細胞，遺伝子を用いて製造されるバイオテクノロジー由来製品(生物製剤)においては，通常の治験届による医薬品機構での審査に入る前に，製品そのものの準備過程や製造についての安全性に関する審査，すなわち医薬品における物質としての理化学試験，規格や製造に関する部分での医薬品機構への申請と審査が安全性の「確認申請」として義務づけられている．

以上により，治験と臨床研究という2つの道筋の存在により，日本の臨床試験には5つの特徴があるといえよう[5~7]．

①特に大学の研究者には，臨床試験の実施に際して手続きに混乱がみられる．つまり，大学の研究成果をどのように臨床応用化していけばよいのかという理解に乏しい．また，治験と臨床研究の差異についても，十分に理解していない研究者が多い．これは，医学部を含めた理系学部において，臨床試験や各種関連法規制などをあまり教育してこなかったことも原因と考えられる．

②現在の法規制においては，新規有効成分を用いた臨床研究の実施にあたっては，治験と異なりGCPの遵守が義務づけられていない．患者の立場からは，治験であろうと臨床研究であろうと未承認の新規有効成分を投与されることには変わりないのに，GCP遵守による被験者の保護には差があるのは不自然である．さらに，新規有効成分を用いた臨床研究の実施にあたっては，保険診療と臨床研究とのいわゆる混合診療は認められていない．そのため，医療機関や患者の負担が増大している．

③現在の仕組みにおいては，医薬品機構の審査事例が蓄積しない．医薬品機構

は企業から提出される治験のみを中心に審査する．まだ萌芽的な研究シーズの段階で実施される臨床試験は，大学などの研究機関が公的研究費を獲得することにより実施される．ところが，医薬品機構はこういった先端的な臨床研究の審査を行っていないため，開発の歴史や評価の過程を理解しにくく，審査事例が蓄積しない．そのためにさまざまな新規のチャレンジの審査の経験を積むことができず，企業からの治験という開発段階となってから提出された審査が遅れてしまうこともあるようである．現状の医薬品機構の人的リソースは米国FDAに比べて10分の1以下であり，更なる人員強化と，大学や企業からの医師を含む有識者人材の受け入れ，さらに法的執行力の強化，すなわち独立行政法人ではなく政府省庁(内局)としての対応も必要であると考えられる．

④医薬品機構は企業から提出される治験のみを中心に審査するが，大学など研究機関やその他の医療施設で行われている新規医薬候補品を用いた臨床研究と合わせて一元的に対応していないため，日本においては臨床試験の国内データベースが完備されていない．最近，国内でも臨床研究の登録センターが整備されつつあるが，そもそも，データベースがFDAのような中央行政機関による一括管理をされていないので，臨床試験の進捗状況や臨床研究の科学的レベルの掌握がなされていない．

⑤臨床研究で新規医薬候補品の臨床試験を実施しても，通常その臨床データは国内外の行政当局からはGCPに則る科学的データとはみなされず，以後開発の進行のためにはその後で治験を実施し直さなければならない．そのため，一元化された治験として臨床試験を行う場合と比較して臨床試験のスタートから終了までに時間がかかり，特許の取得から実用化後の商業年数が必然的に減少してしまう．大学などの研究機関で研究された成果の応用化を，臨床研究ののちに製薬企業が開発を継承するインセンティブも失われてしまう．

上述のように，臨床研究と治験の2つの臨床試験をめぐる行政対応と手続きは複雑であり，臨床応用という共通課題を促進するためには，今後我が国の認可行政において医薬品機構の抜本的なあり方の見直しと強化，あるいは医薬品医療機器庁(仮)の設立などを含んだ改革が必要であると思われる．すなわち，新規医薬候補品を用いた臨床研究と治験という区別をなくし，臨床試験を一本化し，医薬品機構にて全面的な科学的審査と開発の支援を企業のみならず大学などアカデミア

に対しても行うような人員や制度の強化が必要と思われる.

5. 医薬品の安全性の評価と薬剤疫学

薬剤疫学という学問は，臨床疫学と臨床薬学にまたがる新しい分野として1980年代に米国で確立した新しい学問である．その研究領域は，医薬品市販後の安全性監視(ファーマコビジランス)，医薬品の効果や副作用に関するアウトカムリサーチ，医薬品の経済性研究，医薬品の安全性評価のためのレギュラトリーサイエンス，医薬品行政の関連法規・ガイドラインの策定に関わる研究と幅広い．我が国においては，これらすべての領域にわたって層の厚い研究者と理解者がいるというわけではなく，まだまだ裾野の拡大と更なる分野の振興が望まれるところである[8].

古典的な薬剤疫学の研究領域としては，いわゆるフェーズ4といわれるような市販後の安全性監視(ファーマコビジランス)，市販後臨床試験(Post Marketing Surveillance)に代表される，医薬品の適正使用調査や疫学研究が中心的である．フェーズ1, 2, 3といった市販前の臨床試験段階では，介入研究として対象患者を限定した環境の中で試験が実施される．そのため，実際に医療の現場で多様な合併症や年齢などのバックグラウンドを有する患者に処方された際の反応性(リアルワールドの事象)を予想できない．これが市販前臨床試験の限界と考えられている．実際の医療の現場で薬剤が使用された際の超個性的な副作用や慢性の薬剤反応をきちんと理解するためには，介入研究ではなく，多くの患者を対象とした観察研究を行うことが重要となるのである．現在では，大規模な観察研究を行うための薬剤の反応性の検出(シグナル検出とも呼ばれる)や電子カルテなどによるデータベースの完備などが薬剤疫学の推進のための重要な要因であると考えられている.

6. おわりに：これからの医薬品開発におけるレギュラトリーサイエンスの重要性

本稿では，転換期を迎えている医薬品開発の現状と，安全性・有効性の評価の多様性を解説した．レギュラトリーサイエンスとは，医薬品，食品，環境物質など，人体などに影響がある物質の適正かつ安全な使用のために，その基準値，安全性・有効性の評価，対応，上位では行政施策やシステムのあり方について，実験室での研究(ウェット研究)や社会学的研究・疫学研究(ドライ研究)，臨床研究を通じて検討していく分野である．臨床の現

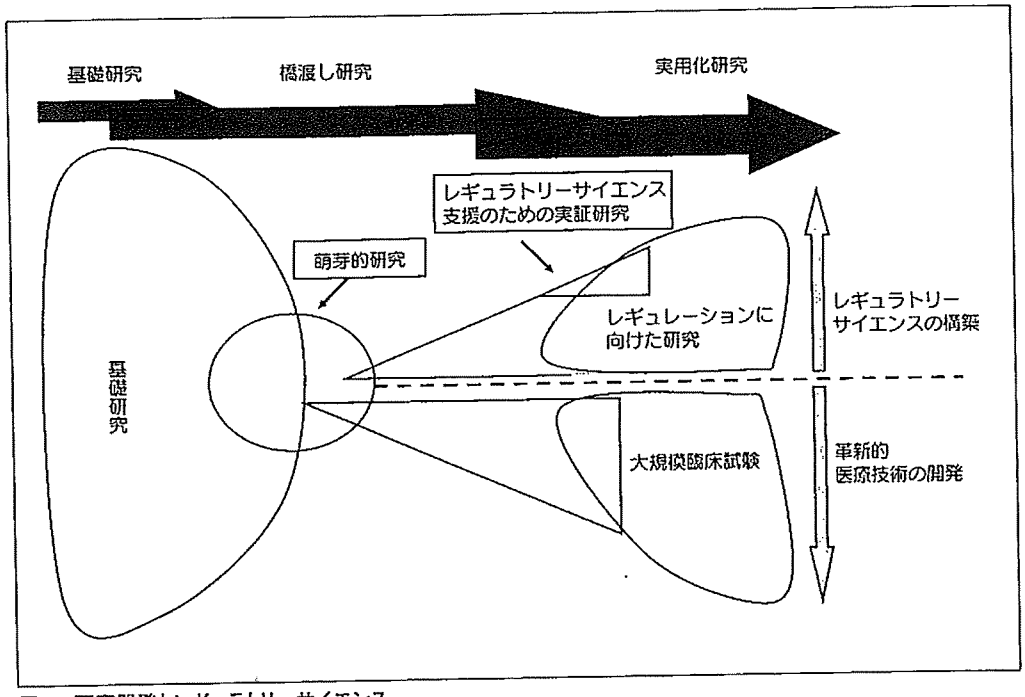

図3　研究開発とレギュラトリーサイエンス

場で用いられる治療用品は，古典的な医薬品，低分子化合物に限らず生物製剤(バイオテクノロジー製剤)，医療機器と多様であり，それぞれの特徴を考えた開発手法，前臨床研究，臨床試験，市販後調査の方法が存在する．したがって，医薬品や周辺分野のレギュラトリーサイエンスに関しては，今後は研究開発から承認後の実際の臨床の現場での使用に至るまでの各段階において手当てがなされていくべきである(図3)．また，行政施策や社会に対してきちんと正確な知見を情報発信していくことも重要である．

さて，レギュラトリーサイエンスというと，和訳直訳すると「規制科学」と訳されることから，規制をしてイノベーションの確度を落としてしまうような印象を与えることもあるが，これはまったくの誤りである．たとえば，再生医療などに用いられる新規性の高い細胞を医療応用化する場合，その細胞が本当に目的臓器を形成するのか，癌化しないのか，感染症のリスクはどうなっていくのかといった懸念事項をクリアしない限り，規制当局からの承認を受けることはできない．そのため，研究開発の各段階において，同じ時間軸でその評価系も構築し，動物実験や臨床試験データから安全性の情報を取得していく，またその科学的結果を行政・規制のガイドラインへと反映し，承認を迅速化していくという考え方は，国際的にも推進されているところである．

我が国においても，レギュラトリーサイエンスの真の重要性を理解し，この領域を産官学ともに推進していかない限りは，せっかく日本発の優れた研究があっても，応用化の出口部分で時間をとられてしまって国際競争に敗北してしまうことになる．特に日本の場合，ライフサイエンス分野では，Investigational New Drug(IND)のシステムの導入，体制の改革も含めて早急に推進する必要があろう．