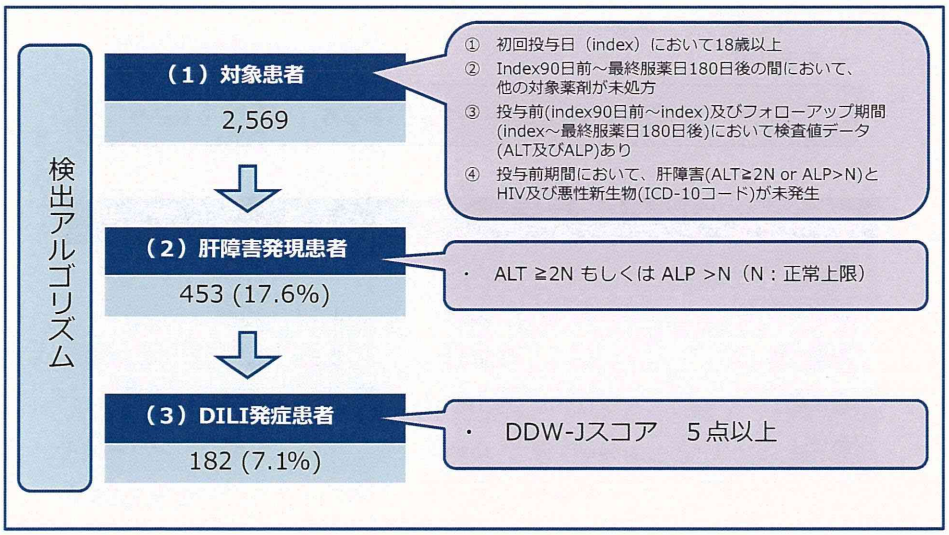
DILI検出アルゴリズムの適用結果

- 対象データ：浜松医大病院　2007年4月から2012年3月末まで（5年間）
- 対象薬剤　：CAM、AZM、LVFX、MFLX



DILI発症リスク因子の評価

○　背景因子の比較

患者背景	単位	DILI発症例 n=182		DILI未検出症例 n=2,387		*P*値
年齢	歳（SD）	65.6	±14.4	61.0	±16.5	0.0007
55歳以上	人（%）	145	(80.0%)	1,690	(70.8%)	0.0107
70歳以上	人（%）	76	(41.8%)	847	(35.5%)	0.0890
男性	人（%）	116	(63.7%)	1,271	(53.3%)	0.0062
投与日数	日（SD）	17.2	±46.3	22.1	±120.8	0.7690
長期投与	人（%）	64	(35.2%)	769	(32.2%)	0.4127
高用量	人（%）	7	(3.9%)	46	(1.9%)	0.0791
糖尿病	人（%）	16	(8.8%)	222	(9.3%)	0.8194

平均値に対してはMann-Whitney U検定、割合に対してはカイ二乗検定

(注) CAM、LVFX、MFLXでは8日以上を、AZMは4日以上を「長期投与」と定義

(注) CAM、LVFX、MFLXについては各薬剤の標準的な用法用量（CAM·MFLX 400mg/日、LVFX 500mg/日）を超える場合、AZMについてはSR成人用ドライシロップ2g使用患者（投与初期の薬物動態を高めた単回投与の製剤）では2,000mg/日を越える場合、それ以外では500mg/日を越える場合を「高用量」と定義

DILI発症リスク因子の評価

○　調整後のオッズ比

アルゴリズムにより検出したDILI発症例とリスク因子に関する多重ロジスティック回帰分析の結果

・ モデル式

アルゴリズム DILI検出 = 年齢 + 男性 + 長期投与 + 高用量 + 糖尿病

リスク因子	ref.	オッズ比	95%信頼区間	*P*値
年齢（55歳以上）	0-54歳	1.52	1.04 – 2.21	0.0294
性別（男性）	女性	1.48	1.08 – 2.03	0.0149
長期投与	なし	1.11	0.81 – 1.53	0.5238
高用量	なし	1.88	0.83 – 4.25	0.5238
糖尿病	なし	0.88	0.52 – 1.50	0.6428

(n = 2,569)

薬剤間でのDILI発症リスクの比較

○　背景因子の比較

患者背景	単位	CAM (ref.) n=524		AZM n=177		LVFX n=1,551		MFLX n=317	
DILI発症	人（%）	30	(5.7%)	17	(9.6%)	106	(6.8%)	29	(9.2%)
年齢	歳（SD）	59.5	±16.4	57.8	±18.6	61.8	±16.1	64.2	±16.0
55歳以上	人（%）	356	(67.9%)	115	(65.0%)	1,116	(72.0%)	248	(67.9%)
70歳以上	人（%）	162	(30.9%)	58	(32.8%)	577	(37.2%)	126	(39.8%)
男性	人（%）	249	(47.5%)	77	(43.5%)	859	(55.4%)	202	(63.7%)
投与日数	日（SD）	66.1	±251.2	3.5	±4.2	11.6	±23.5	8.4	±6.6
長期投与	人（%）	215	(41.0%)	24	(13.6%)	493	(31.7%)	101	(31.9%)
高用量	人（%）	38	(7.3%)	0	(0%)	10	(0.6%)	5	(1.6%)
糖尿病	人（%）	30	(5.7%)	6	(3.4%)	180	(11.6%)	22	(6.9%)

(注) CAM、LVFX、MFLXでは8日以上を、AZMは4日以上を「長期投与」と定義

(注) CAM、LVFX、MFLXについては各薬剤の標準的な用法用量（CAM·MFLX 400mg/日、LVFX 500mg/日）を超える場合、AZMについてはSR成人用ドライシロップ2g使用患者（投与初期の薬物動態を高めた単回投与の製剤）では2,000mg/日を越える場合、それ以外では500mg/日を越える場合を「高用量」と定義

薬剤間でのDILI発症リスクの比較

○　調整後のオッズ比

アルゴリズムにより検出したDILI発症例とリスク因子に関する多重ロジスティック回帰分析の結果

・ モデル式

アルゴリズム DILI検出 = 薬剤 + 年齢（55歳以上） + 男性

薬剤	対照群	n	オッズ比	調整後* オッズ比	95%信頼区間	*P*値
AZM	CAM	701	1.75	1.84	0.98 – 3.45	0.0576
LVFX	CAM	2,075	1.21	1.16	0.76 – 1.77	0.4891
MFLX	CAM	841	1.66	1.39	0.81 – 2.40	0.2339

＊ 年齢（55歳以上）及び性別で調整

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具体的な研究課題

（1）副作用検出アルゴリズムの構築

- 臨床検査値を利用した副作用検出
  - ヘパリン起因性血小板減少症（HIT）
- 臨床スコアリングシステムを利用した副作用検出
  - 薬剤性肝障害（DILI）

（2）行政施策の医療現場における反映・効果の確認

- 添付文書改訂の事例

クロピドグレル と オメプラゾール の併用注意

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クロピドグレル と オメプラゾール の併用注意

2010年4月　添付文書改訂

改訂の背景

- クロピドグレルはCYP2C19等により活性代謝物に代謝されるが、CYP2C19のPM群において作用低下の報告がある
- 「併用注意」の項において、薬物代謝酵素（CYP2C19）を阻害する薬剤としてオメプラゾールが挙げられ、クロピドグレルの作用が減弱するおそれがあると記載されている
- なお、同じPPIであるランソプラゾール及びラベプラゾールについてはCYP2C19を介したクロピドグレルとの相互作用に関する十分な情報がないことから、本行政措置はPPIの中でオメプラゾールに限定されている

（参考）ランソプラゾールはCYP2C19の他にCYP3A4による代謝を受け、ラベプラゾールは主に非酵素的な代謝経路をもつ

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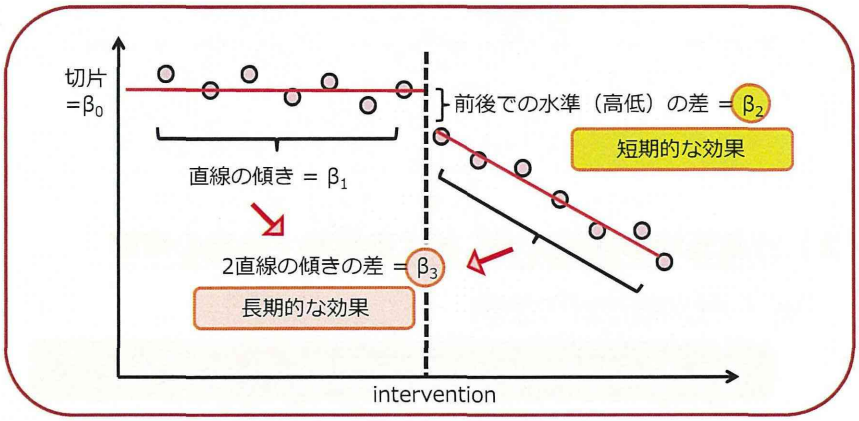
Interrupted time series (ITS) 回帰分析

- モデル式

$$Y_t = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 P + e_t$$

- T：観察期開始時からの時間
- D：interventionの前後をあらわすダミー変数
- P：interventionからの時間
- e：時間 t におけるモデルでは説明されない不規則変動



オメプラゾール併用群 vs 他のPPI併用群

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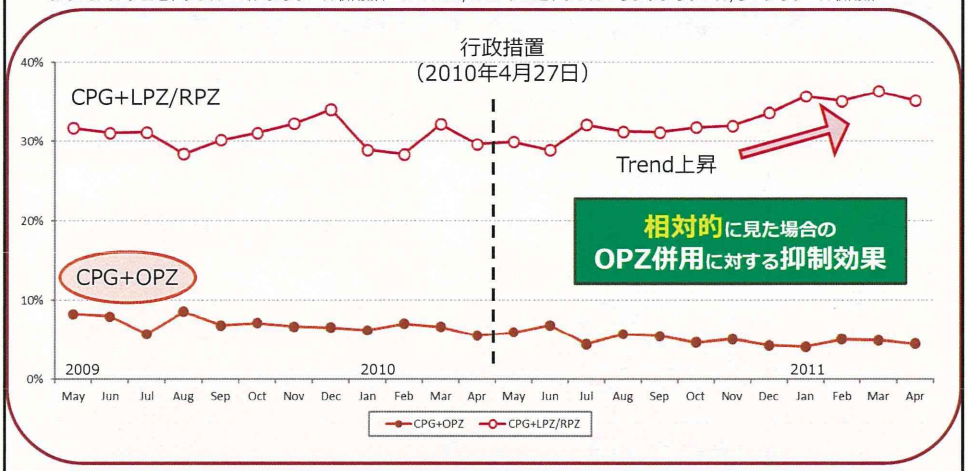
● クロピドグレル処方患者におけるオメプラゾール 又は 他のPPIの併用割合についての月ごとの時系列プロット及びITS回帰分析の結果（浜松医大・東大・香川大・九大４病院統合データ）

CPG+OPG: クロピドグレル＋オメプラゾール併用群、 CPG+LPZ/RPZ: クロピドグレル＋ランソプラゾール/ラベプラゾール併用群



薬剤群	パラメーター	係数	標準誤差	P値
CPG+LPZ/RPZ	Trend change β_3	0.60	0.16	0.0017

新規患者に限定した部分集団解析

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● クロピドグレル処方患者におけるオメプラゾール 又は 他のPPIの併用割合についての月ごとの時系列プロット及びITS回帰分析の結果（浜松医大・東大・香川大・九大４病院統合データ）

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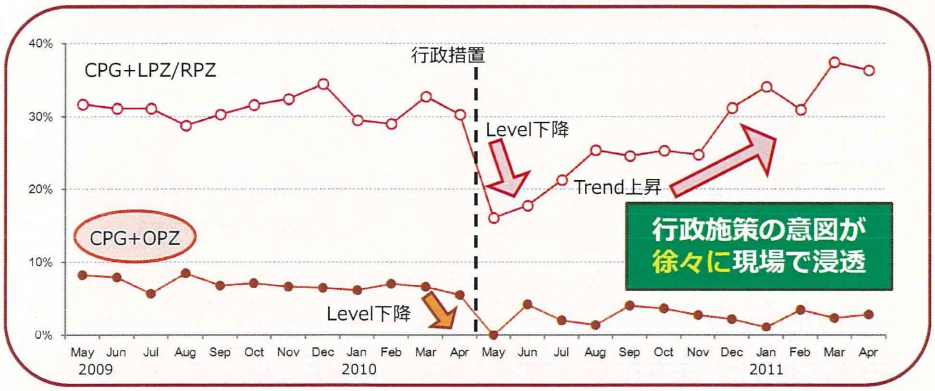

薬剤群		パラメーター	係数	標準誤差	P値
CPG+LPZ/RPZ	新規患者	Level change β_2	-16.03	1.55	<.0001
		Trend change β_3	1.84	0.22	<.0001
CPG+OPZ	新規患者	Level change β_2	-3.87	0.89	0.0003

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データベースの種類による特徴

	病院情報システム（カルテ、オーダリング）	レセプト
情報の範囲	広い 保険外診療も対象（ワクチン等）	保険審査に不要な一部の情報（患者背景、検査値データ等）は含まれない 保険診療の範囲内
情報の精度	高い	月単位と荒く、情報の前後関係が把握できない場合がある レセプト病名や、保険請求上不必要な病名・項目が省略されている可能性
施設間の共通性	各施設単位（共通化が困難）	高い
データの連続性	転院患者の遡及・追跡や、他院受診患者の確認が困難	医療機関横断的なデータ連結が可能
長所	入院や急性の疾患向き	患者条件を揃えることが容易
共通の課題	定型の項目外の情報の利用が困難 診断が複雑・不正確な疾患・副作用には不向き データの二次利用であるためのバイアスが存在し得る可能性	

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日本のセンチネル・プロジェクトの推進に向けて

現　状

○ 大規模な医療情報データベースの構築、そのルール作りが着実に進められている

課　題

○ 現状では日本のデータベースを利用した基礎研究は活発ではなく、特に医師レビューを実施したバリデーション研究が少ない

○ 日本の大規模データベースでの解析に適合する薬剤疫学的手法の評価が必要

○ 日本のセンチネル・プロジェクトの真の成功に向けて

【産】通常の安全対策における大規模データベースの積極的な活用
【官】目的・対象の優先順位付け 及び 計画と成果の一元的な発信
【学】薬剤疫学研究の活発化 及び 人材育成

謝辞

本研究に対しまして多大な御協力・御指導を頂きました

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川上 純一先生、木村 通男先生

に深く感謝いたします。

Detection of Cerebral Infarction Associated with Oral 5-Fluorouracil S-1 and Other Fluoropyrimidines using a Hospital Database

Katsuhito Hori[1], Michio Kimura[2] and Junichi Kawakami[1].
[1]Department of Hospital Pharmacy and [2]Department of Medical Informatics,
Hamamatsu University School of Medicine, Japan.

Background

- There have been several spontaneous reports of the occurrence of cerebral infarction (CI) in patients prescribed with S-1, the combination of tegafur, gimeracil and oteracil potassium, in Japan (~ 50 cases). However, the possibility for the association of the CI occurrence with S-1 or other fluoropyrimidine has not been clarified.

Objectives

- The aim of this study was to detect the CI occurrence after chemotherapy with S-1, UFT (combination of oral tegafur and uracil) and 5-FU injection using a hospital database.

Methods

- Facility: Hamamatsu University Hospital, Japan (613 beds, 1,230 outpatients/day)
- Period: From January 2008 to December 2010
- Data source (patients): All in- and out-patients
- Chemotherapy (tested drugs):
  S-1 (combination of oral tegafur, gimeracil and oteracil potassium), UFT (combination of oral tegafur and uracil) or 5-FU injection
- Definition of CI:
  - ICD-10 code of I63 within 2 months from prescription of tested drugs
  - Symptom of CI
  - confirmation by a diagnosis based on computed tomography (CT) or magnetic resonance imaging (MRI)

  To meet all the above requirements
- Exclusion:
  History of CI before prescription of the tested drugs
- Evaluation:
  - The cases' risk factors for CI; age, sex, smoke, alcohol drinking, complication of hypertension, DM, lipid disorders, and a history of cardiac diseases.
  - Incidence proportion of CI and it's confidential interval after the tested drugs were also evaluated.
- Ethical consideration:
  The protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine following the ethical guideline for epidemiological research, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan (2007).

Results

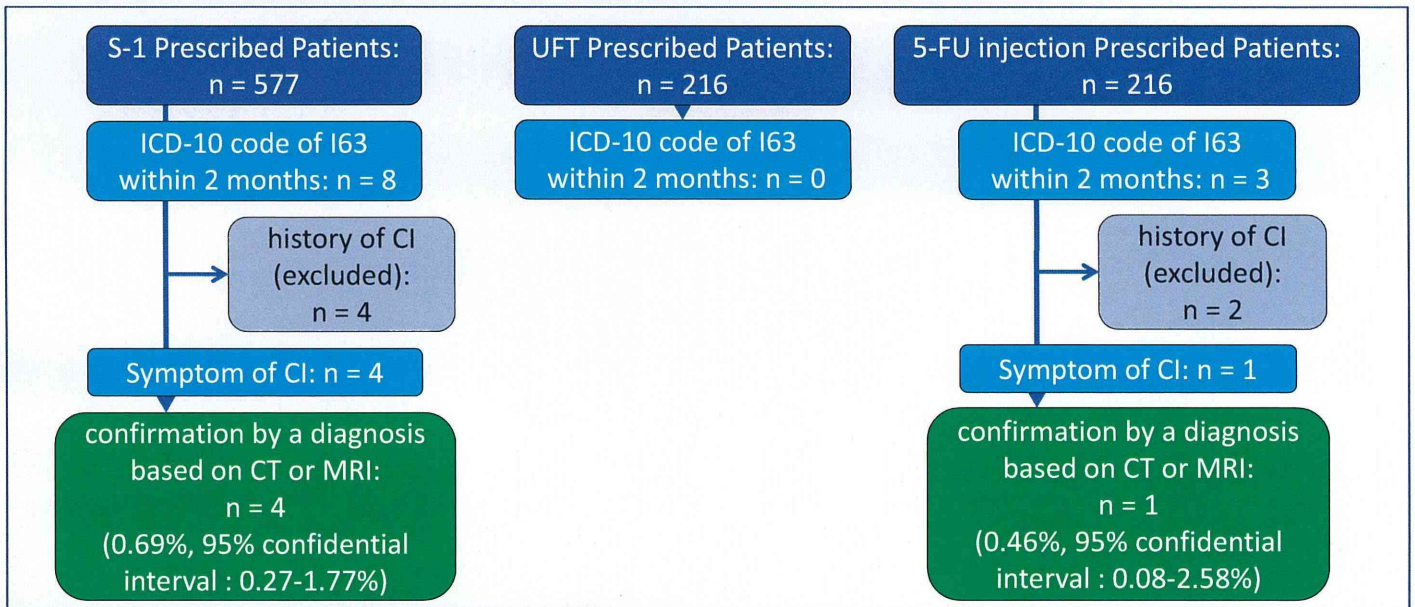

Figure. Definition flow of CI after tested drugs.

Table. Characteristics of Cases

Case #	Tested Drugs	Gender	Age	Cancer	Treatment Days	Concomitant Drugs	Risk Factors of CI *)	S-1 or 5-FU Prescription after CI	Recurrent of CI
1	S-1	male	79	gastric	32	-	smoke	+	-
2	S-1	male	61	pancreas	28	oxycodone lansoprazole loxoprofen prochlorperazine	-	-	
3	S-1	male	59	gastric	28	cisplatin rabeprazole rebamipide	smoke	-	
4	S-1	male	68	gastric lung/brain metastasis	28	famotidine	-	+	-
5	5-FU	male	60	hypo-pharyngeal	3	cisplatin docetaxel loxoprofen fosfomycin	hypertension smoke	+	-

*) Risk factors of CI: smoke, alcohol drinking, complication of hypertension, DM, lipid disorders, and a history of cardiac diseases.

- Incidence proportion of CI after S-1therapy was not significantly higher than that after 5-FU.
- The drugs which can be CI risk were not used concomitantly in the detected 5 cases.

Conclusion

- The occurrence of CI after S-1or 5-FU therapy was able to be detected using a hospital database and confirmed by the diagnostic imaging.

Abstract

Background: S-1, the combination of tegafur, gimeracil and oteracil potassium, is an oral fluoropyrimidine indicated for gastric and colorectal cancer and other carcinomas. There have been a few spontaneous reports of the occurrence of cerebral infarction (CI) in patients prescribed with S-1, however, the possibility for the association of the CI occurrence with S-1 has not been clarified.

Objectives: The aim of this study was to detect the CI occurrence after chemotherapy of S-1, UFT (combination of oral tegafur and uracil) and 5-FU injection using a hospital database.

Methods: A cohort study of the patients of Hamamatsu University Hospital, Japan was designed. An association between S-1 prescription and CI occurrence was searched from all in- and out-patients from January 2008 to December 2010. CI was searched by ICD-10 code of I63, and confirmed by a diagnosis based on computed tomography (CT) or magnetic resonance imaging (MRI). The cases' risk factors of CI were surveyed; age, sex, smoke, alcohol drinking, complication of hypertension, DM, lipid disorders and history of cardiac disease. An association between prescription of UFT or 5-FU and CI was also searched. Incidence rate and 95% confidence interval of CI after these drugs were estimated.

Results: In the research period, S-1 was prescribed in 577 patients. Eight patients had a diagnosis record of CI within 2 months after the first prescription of S-1. By the diagnostic imaging, 4 patients were confirmed as the cases with CI after S-1 therapy (0.69%, 95% CI: 0.27-1.77%). CI occurred in 28-32 days from the start of S-1. All cases were male and 59-79 years old. Although 2 cases had a history of smoking, all cases had no other risk factors for CI. UFT was prescribed in 216 patients, and no patients had a diagnosis record of CI within 2 months after the first prescription of UFT. 5-FU was prescribed in 216 patients, and 1 patient was confirmed as a case with CI after 5-FU therapy (0.46%, 95% CI: 0.08-2.58%).

Conclusions: CI occurrence after S-1 and 5-FU therapy was able to be detected using a hospital database and confirmed by the diagnostic imaging.

Disclosures

The project was funded by Health and Labour Sciences Research Grant (the Ministry of Health, Labour and Welfare,) Japan.

There was no personal or financial relationships relevant to this presentation existed during the past 12 months/during the conduct of the study.

Development of a Distributed Research Network in Japan: a Pilot Study on Antiemetics Use for Chemotherapy Induced Nausea and Vomiting

Katsuhito Hori[1, 2], Norihiro Kobayashi[2], Tomomi Kimura[1, 2], Hitoshi Atsumi[3], Akira Nagayama[4], Masako Kondoh[4], Ichiro Noge[4], Midori Kimura[5], Hiroaki Utsugi[5], Tsuyoshi Iwasaki[5], Masaki Nakamura[6], Michio Kimura[1] and Junichi Kawakami[1].

[1]Hamamatsu University School of Medicine, Japan; [2]Pro-Bono Pharmacoepidemiologists Committee in Japan, Tokyo, Japan; [3]Fukuroi Municipal Hospital, Japan; [4]Numazu City Hospital, Japan; [5]Shizuoka General Hospital, Japan and [6]Medical Data Vision, Tokyo, Japan.

Background

- Most of the large hospitals in Japan own computerized order entry and billing systems but little is explored in their usefulness as a secondary data analyses tool.

Objectives

- The objective is to seek the usefulness of the hospital-based standardized ordering/billing systems by organizing a distributed research network and to describe our experiences on using this network for a nationwide, cross-sectional antiemetic utilization survey.

Methods

- Data source (Fig.): Ordering/billing data repository in 35 hospitals in Japan: of which 4 owned a standardized order entry data repository system (D*D) and the rest provided their billing data via Medical Data Vision (MDV) Co., Ltd.
- Data for patients under injectable chemotherapies (CT) during the study period (Jan/1/2010-Jun/30/2011) was extracted locally
- R codes were distributed by principal investigator (PI) to standardize and anonymize data and exclude data which met the exclusion criteria
- R codes were run by each data partner locally
- The local datasets were checked and merged by PI
- The protocol was approved by the local ethics committees following the ethical guideline for epidemiological research, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health Labuor and Welfare, Japan (2007).

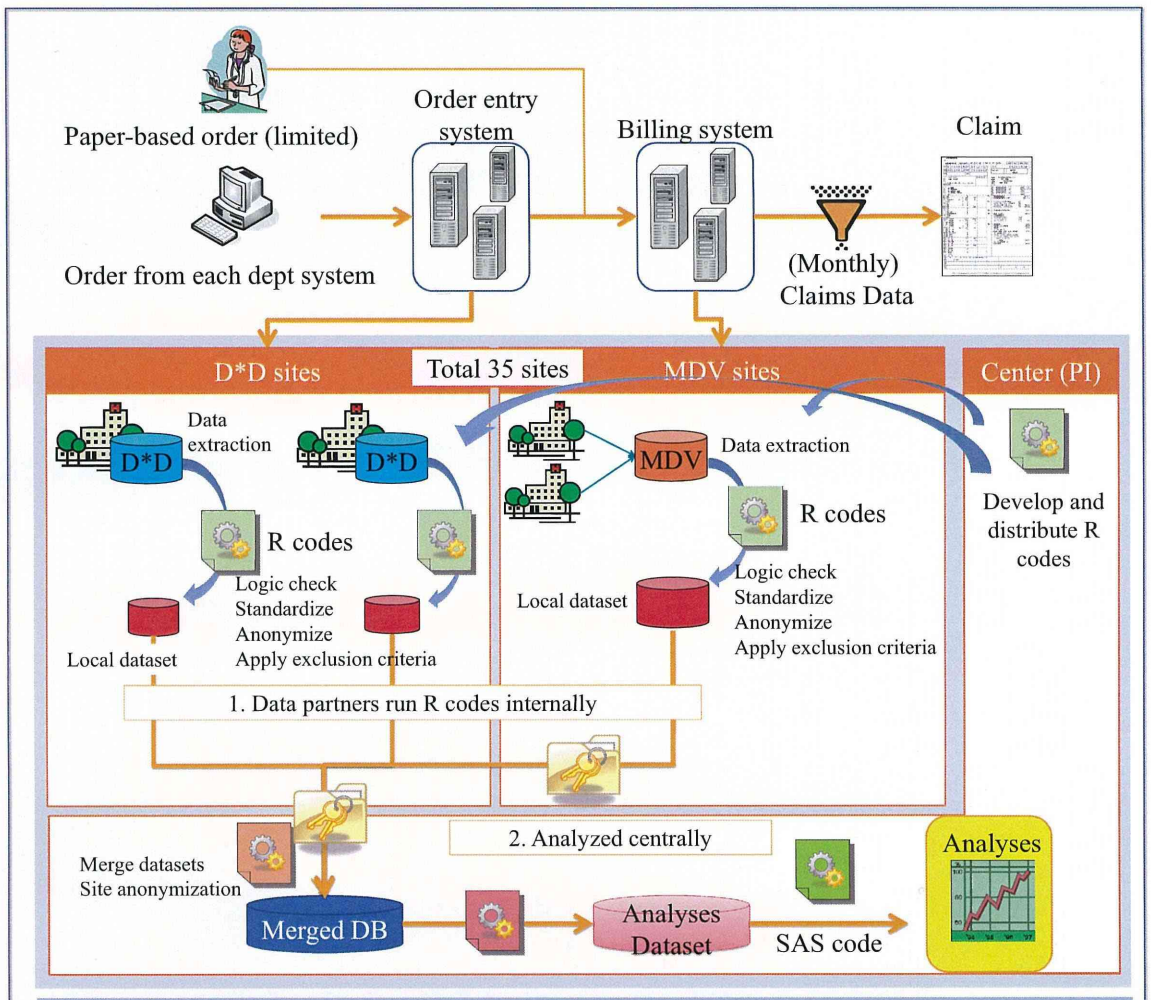

Fig. Distributed Research Network System for this study.
D*D, hospital-based standardized order entry data repository system; MDV, Medical Data Vision Co., Ltd.

Results & Discussion

Table. Major issues and resolution on data processing

Error detection	Cause of issue	Resolution
Memory overloaded	MDV dataset was too huge	Divided into several datasets
Error at data loading with CSV (comma-separated values) format	Comma (,) was used as part of drug name	Remove the comma from respective data manually before data loading
Error log at merging local datasets	Different date format per site (e.g., yyyy/mm/dd)	Patched the R program
Eyeballing of extracted data	Drug name and code didn't match for a medical product at one D*D site because of the error in the formulary	Manually modified the raw data before being merged
Data size for a specific drug was smaller than expected	Prescription of this drug was out of the ordering system (=paper-based) at two D*D sites	Paper-based records were standardized and added manually
Error at data analysis (one patient cannot be inpatient and outpatient on a same day in our dataset)	When outpatient admitted for emergency occasion, ordering can be recorded both as inpatient and outpatient prescription (should have been deleted manually)	By reviewing individual data carefully (n=3), interpreted prescription records as outpatient data

- A total of 75,222 chemotherapy records for 9,367 patients were obtained within 2 months from the first setup meeting and without a financial support. The most time consuming part was the ethical review at each local site. Central review would have shorten the timeline (1-2 weeks for data collection).
- Major issues and resolutions were summarized in Table.
- In advance of developing R codes, it is essential for data partners 1) to understand their local data characteristics (e.g., data format, possible data values, file format and character encoding) and 2) to be familiar with data handling, to some extent.
- By running R codes locally, 1) minimal data was merged for the final analysis, 2) data could be further annonymized e.g., date of birth was transformed into age at CT administration, and 3) local researchers could get back to raw data, as needed.
- CT with different emetic risks by dose/body surface area needed to be excluded only because of lack of demographics (e.g. height and weight)

Conclusion

- We developed a distributed research network in Japan and found it workable, even without an expensive statistical software and data handling skills.
- Researchers who are interested in a nationwide, hospital-based study in Japan can use this network and conduct one with a time-, resource-, and cost-effective manner.

Abstract

Background: Most of the large hospitals in Japan own computerized ordering and billing systems but little is explored in their usefulness as a secondary data analyses tool.

Objectives: The objective is to describe our experiences on developing and implementing a distributed research network of hospital data for a nationwide, cross-sectional antiemetic utilization survey.

Methods: 35 large hospitals with in-/out-patients' detailed daily treatment records were participated: 4 owned a standardized ordering data repository system with the rest provided their billing data via Medical Data Vision Co., Ltd. Data for patients under injectable chemotherapies was extracted locally and standardized into a minimum dataset by distributing R Codes. Datasets were collected with execution logs monitoring any unexpected errors and integrated for analyses.

Results: Records of 75,222 chemotherapy cycles for 9,367 patients between 2010/1/1 and 2011/6/29 were obtained within 2 months from the first setup meeting and without a financial sponsor. By extracting and processing the data, we experienced e.g., missing data, discordance of drug name and code, and partial but systemic paper-based ordering. Some sites allowed a comma for data entry which affected data output in CSV (comma-separated values) format. All the issues were manageable and valuable to improve the system for secondary data use.

Conclusions: The network was workable even without an expensive statistical software and data handling skills. Master agreement and central Ethics Review Committee would shorten the study timeline > 30 days. With a strong local control of data, only minimal required data was centralized, assuring data holders' participation. This network, however, is applicable for selected research questions: linking with other data sources will enable to explore wider variety of clinical researches.

Disclosures

The project was not funded. There was no personal or financial relationships relevant to this presentation existed during the past 12 months/during the conduct of the study.

Development of an Algorithm for Detecting Heparin-Induced Thrombocytopenia and Assessment of the Risk Factors using a Medical Information Database [180]

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【 Abstract 】

Background: A new era of pharmacovigilance is coming using the electronic medical information data systems that are widely spread in most hospitals in Japan.

Objectives: To promote pharmacovigilance activities using a medical information database (MID), we aimed to develop and validate a novel algorithm for detecting heparin-induced thrombocytopenia (HIT), and to assess possible risk factors for HIT.

Methods: This study was performed using a standardized MID in University Hospital of Hamamatsu University School of Medicine (Shizuoka, Japan) which covers health records of approximately 200 thousand patients. Patients who were treated with unfractionated heparin (UFH) together with proper platelet count testing from 1st April 2008 through 31st March 2012 at the Hospital were included. Patients receiving anti-cancer drug therapy within 4 weeks before the UFH administration were excluded. We developed a HIT detection algorithm based on the time-course information of platelet count and the diagnostic information to exclude pseudo-HIT. Definite diagnoses of HIT were made from medical record review by a skilled hematologist, and algorithm performance was assessed using positive predictive value (PPV). Possible risk factors for HIT development were evaluated by multivariate logistic regression analysis.

Results: The current algorithm detected 47 patients with suspected HIT in the source population (n=2,875). Of these, 41 were identified as definitive HIT after the medical record review. The PPV for the algorithm was 87.2% (95% CI: 74.8-94.0%), and the frequency of definitive HIT was 1.4%. Longer-term treatment (more than 3 days) was identified as a risk factor for HIT, with an odds ratio of 5.38 (95% CI: 2.35 to 12.32) for definitive HIT.

Conclusions: We successfully developed a novel, high PPV detection algorithm for HIT, and identified possible risk factor for HIT. Our results support the utility of MIDs for improving pharmacovigilance and related scientific research.

【 Conflict of Interest Statement 】

- This study was supported by the Program for the Promotion of Studies in Health Science of the Ministry of Health, Labour and Welfare of Japan.
- The authors' research was conducted independently of the funding organization, and all authors declare no conflict of interest relevant to this study.

【 Background 】

- pharmacovigilance using a medical information database (MID) has become crucial
- Heparin-induced thrombocytopenia (HIT) can occasionally cause severe thrombosis
- Clinical features of HIT in large populations, including its frequency and associated risk factors, remain unclear

【 Objectives 】

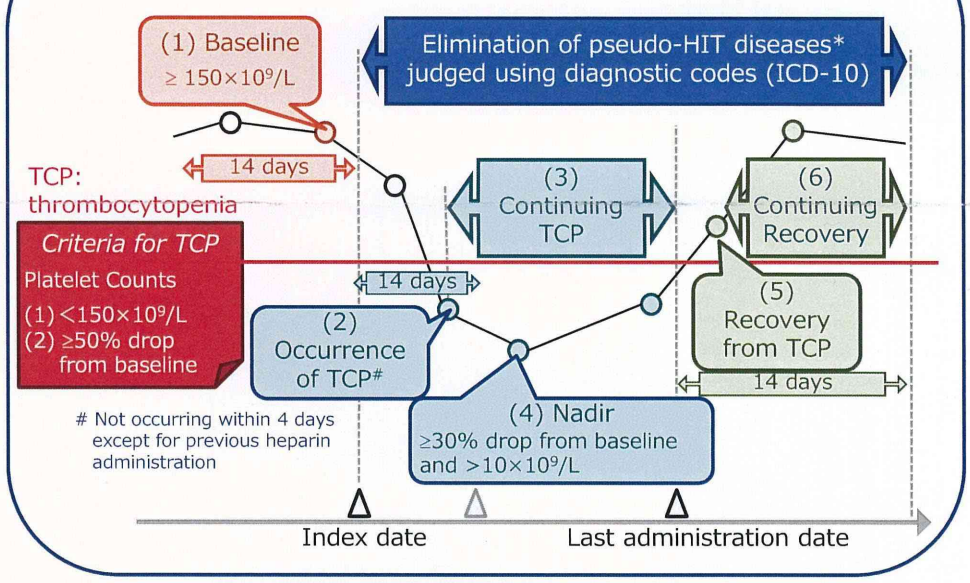
To promote pharmacovigilance activities using MID, we aimed to;

- *Develop an algorithm for detecting HIT*
- *Validate the algorithm*
- *Assess possible risk factors for HIT*

【 Methods 】

- *Data source and Ethics*
  - Linkable anonymized data from MID of the Hospital of Hamamatsu University School of Medicine (Shizuoka, Japan), which covered 200,000 patients, were used
  - This study was approved by the ethics committees of both the Hospital of Hamamatsu University School of Medicine and the National Institute of Health Sciences
- *Inclusion Criteria*
  - Treated with unfractionated heparin injection between April 1, 2008 and March 31, 2012
  - Having tests for platelet count both within two weeks prior to and after the index date (first date of administration)
  - Not treated with anti-cancer drug within 4 weeks before the index date
- *HIT Detection Algorithm* (see Figure)
  This algorithm was developed based on;
  - **6 criteria on platelet-count behavior over time** [(1)-(6) in Figure]
  - **Differentiation from pseudo-HIT diseases** by using ICD-10 codes*
- *Validation Study*
  - A hematologist ultimately made a definite diagnosis of HIT by comprehensive review of medical records with the aid of 4Ts scoring**
- *Assessment of Risk factors for HIT*
  - Multivariate logistic regression analysis was performed for the assessment
  - Age, gender, medical history, treatment duration, hepatic dysfunction, renal dysfunction and surgery were included in the model

【 Figure 】 Diagram of HIT Detection Algorithm



* Disseminated intravascular coagulation (D65), anti-phospholipid antibody syndrome and congenital protein C or S deficiency (D68.8), immune thrombocytopenia purpura (D69.3), and thrombotic thrombocytopenia purpura (M31.1)

** Warkentin TE, *et.al.* Curr Hematol Rep, 2003;2:148-157.

【 Results 】

- *Selection Chart for Definitive HIT and Performance of the Algorithm*

Source Population	(1)-(6) in Figure	Extracted Population [Judged by Platelet Count]	Excluding Pseudo-HIT	Suspected HIT	Validation Study	Definitive HIT	PPV (95% CI)
		Detection by using Algorithm				Medical Record Review	
n=2,875	→	n=58	→	n=47	→	n=41 (1.4%)	87.2% (74.8-94.0%)

- *Patient characteristics in definitive HIT and non-HIT groups*

Characteristics		Definitive HIT n=41	Non-HIT n=2,834	P*
Age ≥ 65 yrs	n (%)	26 (63.4%)	1,539 (54.3%)	0.2449
Female	n (%)	14 (34.2%)	1,190 (42.0%)	0.3121
Medical history (heparin)[a]	n (%)	6 (14.6%)	437 (15.4%)	0.8900
Treatment duration ≥ 4 days	n (%)	34 (82.9%)	1,320 (46.6%)	<.0001
Hepatic dysfunction[b]	n (%)	4 (9.8%)	599 (21.1%)	0.0756
Renal dysfunction[c]	n (%)	14 (34.2%)	1,011 (35.7%)	0.8393
Surgery[d]	n (%)	15 (36.6%)	918 (32.4%)	0.5691

- *Multivariate logistic regression analysis on HIT development*

Variable	Reference	Odds ratio	95% CI	P
Age ≥ 65 yrs	< 65	1.38	0.70 – 2.70	0.3565
Female	Male	0.83	0.43 – 1.61	0.5830
Medical history (heparin)[a] –Yes	No	1.00	0.41 – 2.42	0.9985
Treatment duration ≥ 4 days	1-3 days	5.38	2.35 – 12.32	<.0001
Hepatic dysfunction[b] –Yes	No	0.44	0.16 – 1.26	0.1253
Renal dysfunction[c] –Yes	No	0.82	0.42 – 1.63	1.63
Surgery[d] –Yes	No	0.95	0.49 – 1.82	0.8662

[a] Exposure to any heparin within 100 days before the index date. [b] >2×Upper Limit of Normal (ULN) of ALT, AST or total bilirubin at the last test date before the index date.
[c] >ULN of serum creatinine or blood urea nitrogen at the last date before the index date. [d] Performed from 3 days before the index date to the last administration date.
* Chi-square test.

【 Conclusions 】

- We have developed a novel, high-PPV (87.2%) algorithm for the identification of HIT using a hospital MID
- Important clinical features of HIT, including the frequency of HIT (1.4%) and longer-term use as a risk-factor have been identified
- Our results support the utility of MIDs for improving pharmacovigilance

[REFERENCE: Hanatani T, *et. al.* J Clin Pharm Ther. 2013 Jul 12. doi: 10.1111/jcpt.12083.]