HIT検出アルゴリズムの適用結果

- 対象期間：2008年4月から2012年3月末まで（４年間）
- 対象薬剤：未分画ヘパリン

（１）対象患者

2,875

↓

（２）検査値による抽出患者

58（2.0%）

↓

（３）検査値＋病名による抽出患者

47（1.6%）

播種性血管内凝固症候群(DIC)、抗リン脂質抗体症候群(APS)、先天性プロテインC/S欠損症、血栓性血小板減少性紫斑病(TTP)又は特発性血小板減少性紫斑病(ITP) の「確定診断例」は除外

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HIT疑い症例

↓

（３）検査値＋病名による抽出患者

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播種性血管内凝固症候群(DIC)、抗リン脂質抗体症候群(APS)、先天性プロテインC/S欠損症、血栓性血小板減少性紫斑病(TTP)又は特発性血小板減少性紫斑病(ITP) の「確定診断例」は除外

HIT疑い症例・未検出症例別の背景比較

	単位	HIT疑い症例	HIT未検出症例	*p*値
症例数	人	47	2,828	
年齢 65歳以上	人（%）	29 （61.7%）	1,536 （54.3%）	0.3131
男性	人（%）	31 （66.0%）	1,640 （58.0%）	0.2723
100日前投与あり	人（%）	7 （14.9%）	436 （15.4%）	0.9214
投与日数# 4日以上	人（%）	38 （80.9%）	1,316 （46.5%）	<.0001
肝機能障害あり	人（%）	8 （17.2%）	595 （21.0%）	0.5022
腎機能障害あり	人（%）	15 （31.9%）	1,010 （35.7%）	0.5896
手術あり	人（%）	18 （38.3%）	915 （32.4%）	0.3881

全症例における投与日数の中央値は３日

(注) 検定法はカイ二乗検定

(注) 肝機能障害とは開始基準日より前のALT、AST又は総ビリルビンの直近の検査値のいずれかが施設基準値上限の２倍以上に、腎機能障害とは開始基準日より前のクレアチニン又はBUNの直近の検査値のいずれかが施設基準値上限以上になった場合と定義

(注) 手術ありとは開始基準日の3日前から最終投与日の前日までに手術（医科点数表で手術を示すK）の記録のあった場合と定義

HIT発症リスク因子の評価

アルゴリズムにより検出した未分画ヘパリン処方例におけるHIT疑い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 hit検出 = 年齢 + 性別 + ヘパリン類100日前投与 + 投与日数 + 肝機能障害 + 腎機能障害 + 手術

リスク因子	ref.	オッズ比	95%信頼区間	*p*値
年齢（65歳以上）	0-64歳	1.36	0.73 – 2.55	0.3340
性別（女性）	男性	0.83	0.45 – 1.54	0.5484
100日前投与 あり	なし	1.04	0.46 – 2.36	0.9269
投与日数 4日以上	1-3日	4.74	2.26 – 9.94	<.0001
肝機能障害 あり	なし	0.84	0.39 – 1.84	0.6687
腎機能障害 あり	なし	0.72	0.38 – 1.39	0.3295
手術 あり	なし	1.01	0.55 – 1.86	0.9725

（n = 2,875）

結果と考察

- 医療情報データベースを用いてHITを検出するアルゴリズムを構築した
- 浜松医科大学病院の医療情報データベース（D☆D）に本アルゴリズムを適用した結果、未分画ヘパリン投与群 2,875例中 47例（1.6%）のHIT疑い症例を検出した
- 報告されているHITの発症頻度（0.5～5%程度）から考えると、一定水準のアルゴリズムの条件設定が行えたものと考えられる
- 未分画ヘパリン投与群に対してHITのリスク因子の影響を評価したところ、「投与日数」が有意な因子として同定された

本研究の結果は、一病院の調査であるため症例数等の限界が存在するものの、HITについての臨床的特性及びリスク因子の影響の一端を明らかにするだけでなく医療情報データベースを利用した副作用評価の実行可能性を支持するものである

医療情報データベースを用いた医療現場における行政施策の反映の確認

○ 花谷 忠昭[1)]、佐井 君江[1)]、堀 雄史[2)]、川上 純一[2)]、木村 通男[3)]、斎藤 嘉朗[1)]

1) 国立医薬品食品衛生研究所 医薬安全科学部　2) 浜松医科大学医学部附属病院 薬剤部　3) 浜松医科大学医学部附属病院 医療情報部

【目的】

現在、本邦では大規模な医療情報データベース（DB）の整備事業（日本のセンチネル・プロジェクト）が進められており、この基盤整備によって、より迅速で適切な安全対策措置の実施が可能となることが期待されている。
しかしその実現には、予め薬剤疫学的手法の確立とその有用性の検証が必要となるため、本研究では、浜松医科大学医学部附属病院（浜松医大病院）の保有する医療情報データベース（D*D）を活用し、過去の安全対策措置2件について疫学的な分析・評価を行った。

【解析手法】Interrupted time series (ITS) 回帰分析

- モデル式

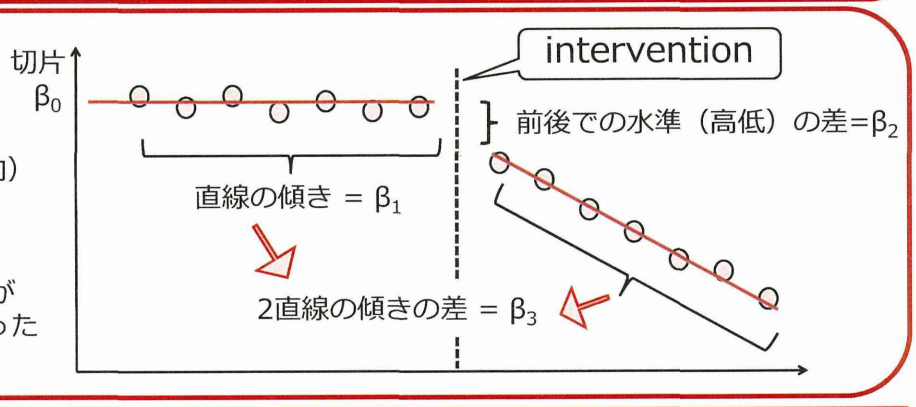
$$Y_t = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 P + e_t$$

  - 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（intervention前は0、後は1をコード）
  - 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

- 評価

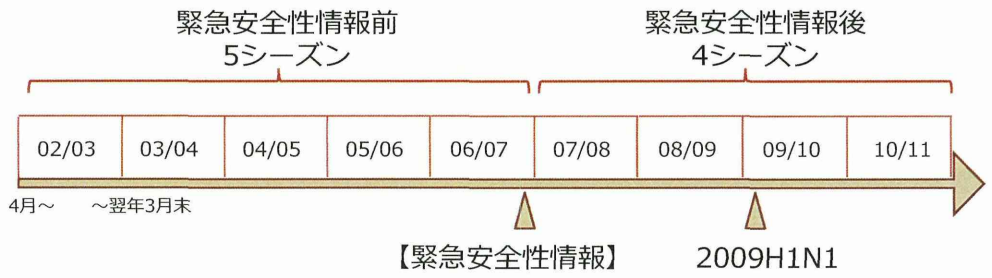
  β_1：intervention前の平均変化率（傾向）
  β_2：intervention直後の水準の変化
  β_3：interventionによる傾向の変化

  - 本研究においては β_2 又は β_3 に有意差が認められた場合、行政措置の影響があったと評価した

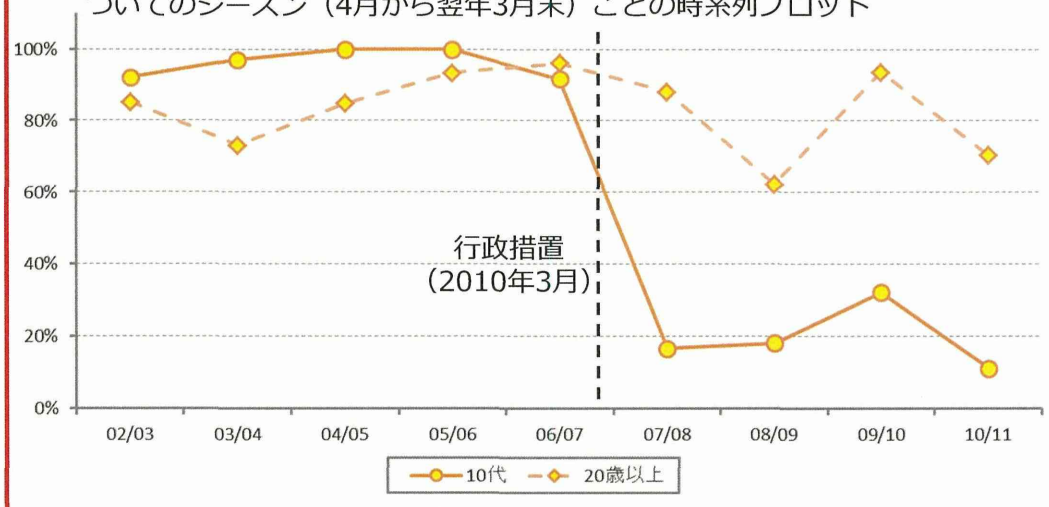


【結果】
『事例①』10代へのオセルタミビル投与の原則差し控え

- 2007年3月　緊急安全性情報発出 及び 添付文書改定
- 本剤服用後の異常行動の発現を受けて、「警告」の項において、10代の患者に対してはハイリスク患者以外への投与を原則差し控えるよう注意喚起を行った。



- ノイラミニダーゼ阻害薬投与患者におけるオセルタミビル処方割合についてのシーズン（4月から翌年3月末）ごとの時系列プロット

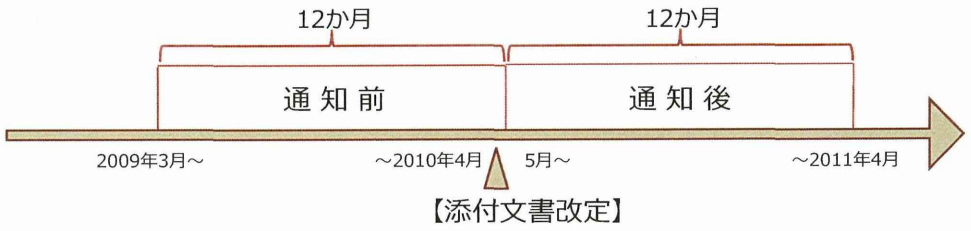


- 年齢群ごとのオセルタミビル処方割合に対するITS回帰分析

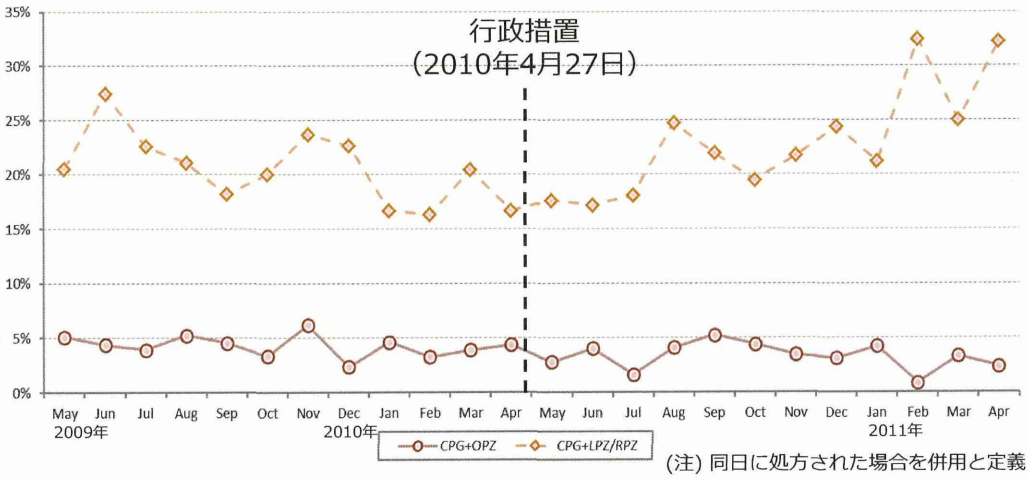
年齢群	ﾊﾟﾗﾒｰﾀｰ	係数	標準誤差	95%信頼区間	p値
10代	β_1	0.21	2.46	-6.13 to 6.54	0.937
	β_2	-76.38	11.30	-105.41 to -47.34	**0.001**
	β_3	-0.49	4.27	-11.46 to 10.49	0.914
20歳以上	β_1	4.22	3.93	-5.89 to 14.33	0.333
	β_2	-10.85	18.02	-57.17 to 35.48	0.573
	β_3	-6.43	6.81	-23.94 to 11.08	0.388

【結果】
『事例②』クロピドグレルとオメプラゾールの併用注意

- 2010年4月　添付文書改定
- クロピドグレル（CPG）はCYP2C19等により活性代謝物に代謝されるが、CYP2C19のPM（Poor Metabolizer）群では本剤の作用が低下するとの報告
- 「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（OPZ）が記載された。



- CPG処方患者におけるOPZ又は他のPPI (ランソプラゾール(LPZ) 又はラベプラゾール (RPZ)) 併用割合についての月ごとの時系列プロット



(注) 同日に処方された場合を併用と定義

- CPG処方患者におけるOPZ又はLPZ/RPZ併用割合に対するITS回帰分析

投与群	ﾊﾟﾗﾒｰﾀ	係数	標準誤差	95%信頼区間	p値
CPG+OPZ	β_1	-0.08	0.10	-0.29 to 0.12	0.390
	β_2	0.01	0.95	-1.96 to 1.98	0.989
	β_3	0.006	0.14	-0.28 to 0.29	0.966
CPG+LPZ/RPZ	β_1	-0.54	0.32	-1.21 to 0.12	0.105
	β_2	-1.71	3.13	-8.24 to 4.82	0.591
	β_3	1.56	0.45	0.61 to 2.50	**0.003**

【まとめと考察】

『事例①』浜松医大病院でのノイラミニダーゼ阻害薬投与患者（計1,871例/9シーズン）のオセルタミビルの処方割合に関して、20歳以上の患者では行政施策前後で有意な変化はなかった。一方、10代については、施策導入後には76.4%の減少（p=0.001）が認められた

『事例②』浜松医大病院におけるCPG処方患者（計2,516例/24か月）のうち、OPZ併用（計94例）の割合は行政措置後も変化はなかったが、類薬であるLPZ又はRPZ併用（計551例）の割合については、措置後に1.56%/月の率で増加（p=0.003）が認められた。
CPGとOPZ併用例で行政措置の影響が見られなかった理由として、症例数（平均3.9人/月）の少なさと継続使用者の存在が影響したものと考えられ、より大規模なデータでの解析・評価が必要である。

- 以上の結果は、医療情報DBによる行政措置の定量的評価の実行性を支持し、安全対策措置の迅速な評価を可能とするものと期待される。

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

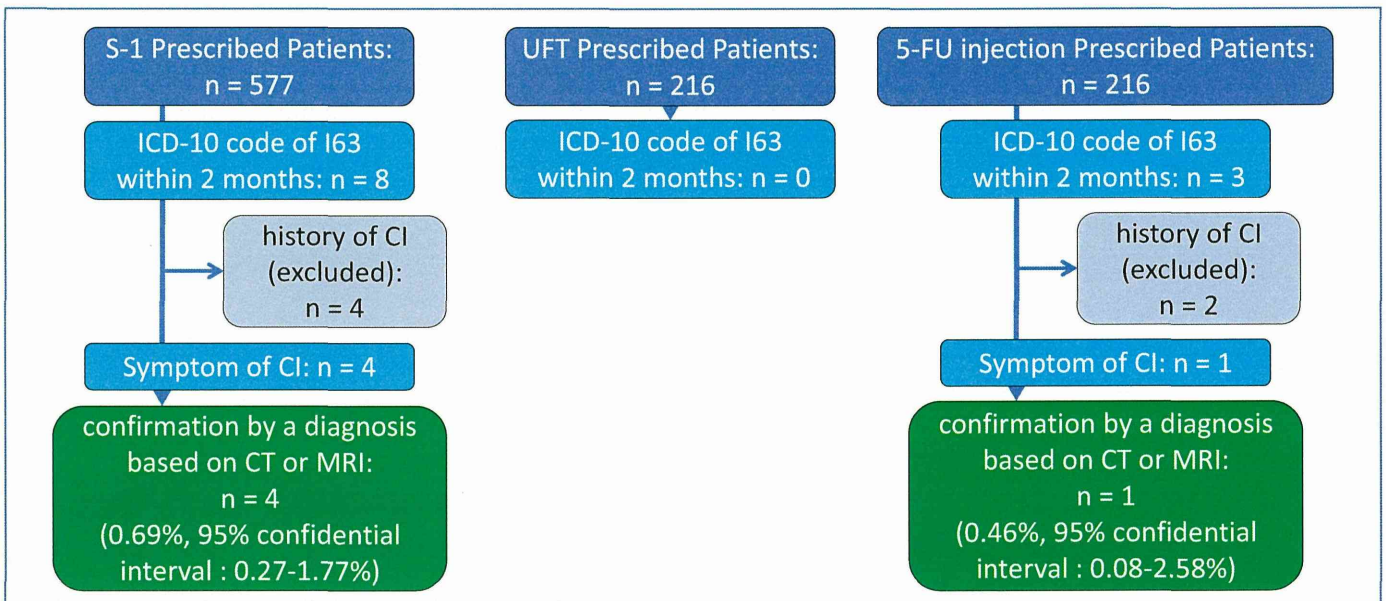


Figure. Definition flow of CI after tested drugs.

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).

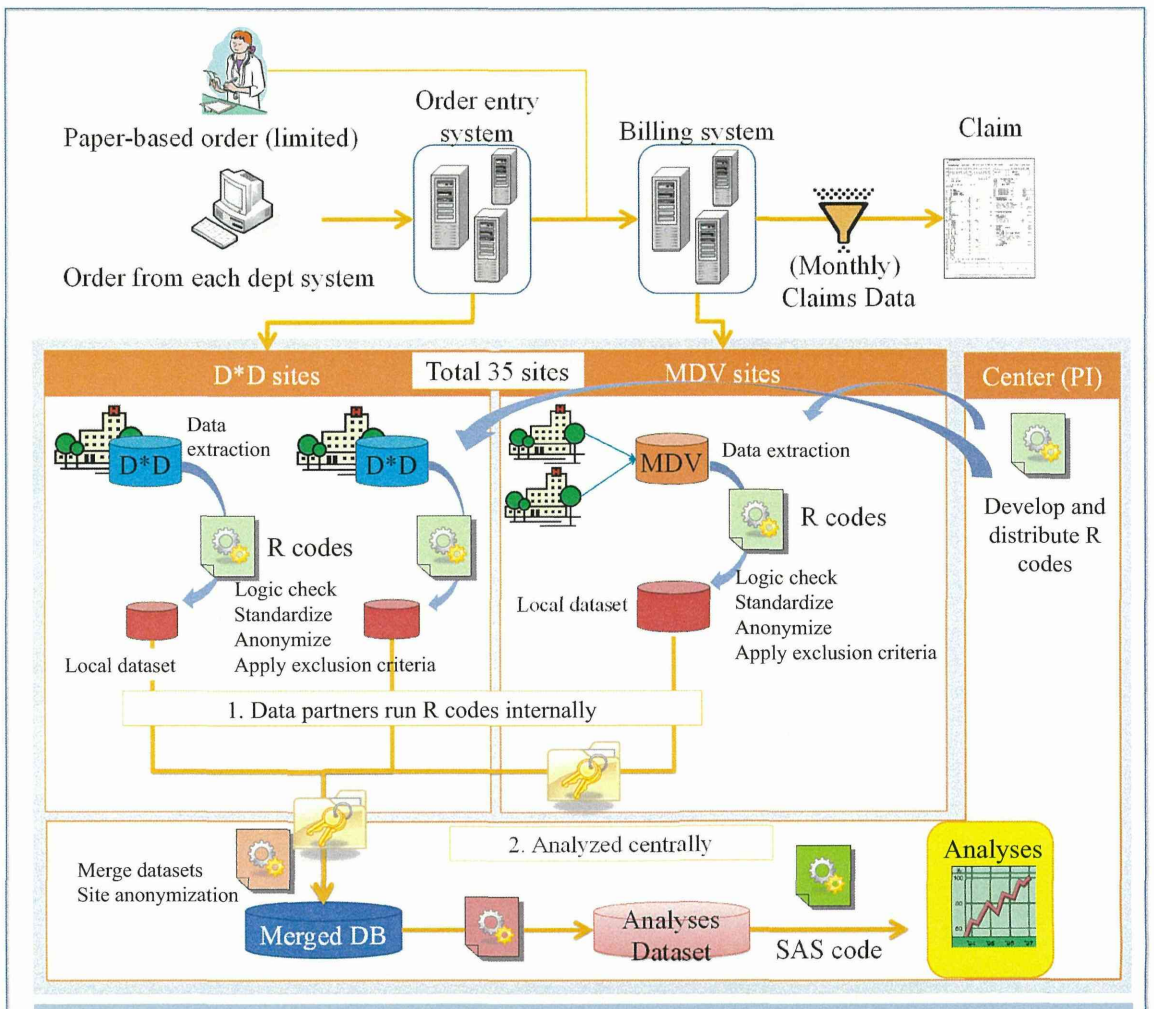


Fig. Distributed Research Network System for this study.
D*D, hospital-based standardized order entry data repository system; MDV, Medical Data Vision Co., Ltd.

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.