【アンケート結果】

施設		A	B	C	D	E	F
Q1 患者	受診	1	1	0	0	1	1
	診療科対応	1	1	0	0	0	1
	電話等窓口	1	1	0	1	1	1
	発行物	1	0	0	0	0	0
	HP	1	0	0	0	0	0
	情報提供活動	0	0	0	0	0	0
	その他	0	0	1	0	1	0

Q2 他院	受診	1	0	0	0	1	1
	診療科対応	1	1	0	1	1	1
	電話等窓口	1	0	0	1	0	1
	発行物	1	0	0	0	0	1
	HP	1	0	0	0	0	0
	情報提供活動	1	0	0	1	1	0
	その他	0	0	1	0	0	0

Q3 更新	印刷物患者向け	0	0	0	1	0	0
	印刷物他院向け	0	0	0	0	1	0
	HP	0	0	1	1	0	1
	掲示患者向け	0	0	0	0	0	0
	掲示職員向け	1	0	0	0	0	0
	勉強会	0	1	0	1	0	0
	その他	0	0	0	0	0	0

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分担研究報告書

医療施設間情報伝達手段の実態調査

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研究要旨

がん診療に不可欠な情報の一つである病理診断関連情報伝達の確度を明らかにすべく、紹介先施設における紹介元施設の病理診断の再検討の実態を分担研究として調査することとした。2006年の1月から9月の間において分担研究者の施設で再検討された病理診断は1,349件あった。原診断書が送付され紹介先施設の電子カルテ上で閲覧可能になっているのは638件（47%）であった。そのうち47件に治療の変更の可能性が高い原診断と再検討診断の不一致が見られ（47/638 7.4%）、さらにその中の14件（2.2%）には良性と悪性の深刻な不一致が見られた。がん診療に不可欠な病理診断に関する情報伝達の確度を確保し適切な治療を行うために、紹介元施設は原診断書や診断に使用された病理標本（または未染色標本）を確実に送付し、紹介先施設では原診断書をカルテ上で閲覧可能とし病理診断の再検討を施行することが重要であると考えられた。

A. 研究目的

本研究の目的は、がん臨床研究に不可欠な症例登録を推進するための患者動態を明らかにし、がん診療の中核病院と地元医療機関との連携により紹介・逆紹介を円滑にするネットワークを作成することである。

がん診療の第一歩は病理診断による確定診断である。診断と治療は一体不可分の関係にあるが、諸般の事情により診断と治療が別々の施設でされる場合も少なくない。たとえばある医療施設で病理診断がついたがんに対する治療が、その施設でできない場合などに、そのがんの治療を得意としている医療施設に患者を紹介する場合などである。分担研究者の勤務する癌研究会は癌研有明病院を有しており多くのがん患者が紹介されている。

そこで、患者そのものでなく、がん診療に不可欠な情報の一つである病理診断関連の情報の動態を明らかにすべく、紹介患者の病理診断に関する情報伝達の確度を精査することとした。具体的な検討項目は、#1. 紹介状や病理標本だけでなく病理診断書そのもののコピーがどの程度紹介先のカルテ上で閲覧可能になっているか、#2. 病理標本の再検討により、治療方針の変更を要する診断の変更がどの程度生じているか、である。

B. 研究方法

2006年の1月から9月までに、癌研病理部において診断の再検討がなされた他院借用標本の総数を病理診断システムにおける検索で明らかにした。紹介元施設の統計を取り特定の紹介ルートの有無を検討した。さらに、電子カルテ上にて原診断書のコピーを参照できる症例に関して、原診断と癌研における診断（以下再検討診断）の差異を検討した。

C. 研究結果

2006年1月より9月までの間に癌研有明病院で受け付けられた病理検体は19,224件であり、そのうち1,349件（7.0%）が他施設にて診断された標本が送付されてきたものであった。紹介元施設数は約600施設であったが、そのうち約400施設が一度のみの紹介であった。

標本借用件数が12件以上の施設が12あり、これらの施設からの標本は203件（15.0%）をしめている。紹介数1位の診療科（296件）では、この12施設からの検体が86件（29.1%）を占めるのに対し，2位の診療科（249件）では、24件（9.6%）のみであった。

1,349件のうち、病理診断書が電子カルテ上で参照可能であったものは638件（47%）であった。レビュー診断と原診断との照合では、治療方針の変更を要すると考えられる診断の不一致が47件認められた。この判断は病理専門医である分担研究者の判断であり、真に診断の変更を有するものか否かの詳細な検討を当該分野のエキスパートと更におこなう予定である。

D. 考察

紹介元施設における病理診断の内容が紹介先施設に正しく伝達されるか否かはきわめて重要なことである。その観点から、電子カルテ上で参照できる紹介元施設での病理診断書が、紹介患者の半分以下にとどまる現状は問題であろう。病理診断には診断にいたるプロセスが微妙なニュアンスで書かれていることがあり、単なる主診断名の伝達ではそれが表現できない場合がある。病理診断書を電子カルテ上で参照できない理由としては二通り考えられた。ひとつは、紹介元施設から病理診断書のコピーが送られてきていない事例で、もうひとつは、コピーは送られてきているが紹介先施設の電子カルテ上に取り込まれていない事例である。ほとんどは前者が原因であると思われる。分担研究者の経験では、後者の事例も明らかに存在するが、頻度などの詳細は今回の検討では把握困難であった。チーム医療の必要性が叫ばれる昨今の状況を鑑みるに、診療に関する重要な情報はすべてカルテ上に保管し情報の共有化に努めるべきであると考える。

紹介元施設数の検討により、科によって特定の紹介ルートの有無に相違がある様子がうかがわれた。これは、紹介元と紹介先の医師同士または科同士の縁故関係が背景にあるものと推察される。

治療方針の変更を伴う診断の不一致は47件に見られた（47/638 7.4%）。このうち33件は、浸潤癌か非浸潤癌かの不一致，がんの悪性度の評価の不一致などである。大きなぶれはないと思われるが、真に治療が異なる事例か否か当該領域の専門家との詳細な検討を更に要すると考えられた。しかしながら、他の14件は良性と悪性の不一致であり、この不一致の重大さは論を待たない。638件中14件（2.2%）という数を多いと見るか少ないと見るかは意見の分かれるところであると思うが、きわめて侵襲性の高い治療の要不要にかかわる不一致だけに病理診断の再検討はやはり必須であると考えられた。そして場合によっては、再生検により更に精度の高い診断をつけることも必要であると思われる。

この結果は、病理医不足問題、およびいわゆる一人病理医問題を考える上でも示唆的なデータであろう。病理専門医は現在約2000人しかおらず、米国と比較して人口あたりの病理専門医数は1/3以下であり、全医師数に占める病理専門医の割合も1/2以下である。さらに、そのうち半数以上が50歳を超えていることから今後減少が見込まれる。日本全国で約9000ある病院のうち、常勤病理専門医の居ない病院は約94%であり、常勤病理医専門医のいる病院の半数強に当たる約330病院においても病理医は一人体制である（日経新聞2006年5月11日）。また、病理診断において、二人以上の病理専門医によるダブルチェックを全検査に実施しているのは病理学会が調査した427施設中84施設（19.7%）に過ぎない（日本病理学会精度管理アンケート調査、2005年）。二人以上の病理医の意見がことなった場合には議論による意見の集約がなされたり、当該領域を専門とする第三者病理医にコンサルトをすることが一般的であるが、がんの病理診断においては2%から7%でそのような事態が生じるものだということになる。したがって、一人病理医体制を強いられている状況下では、そのような本来行われ

るはずの議論や診断変更の機会が恒常的に失われていることを意味している。

今回の検討は、病理診断の再検討が行われた症例を母集団としている。再検討なしで治療される事例、さらに再検討も病理診断書の添付もなく紹介先施設で治療される事例もあると考えられる。その現状の把握も必要であると考えられた。

E. 結論

紹介先での病理診断の再検討において、原診断書がカルテ上で閲覧可能になっている状況は47%であり、そのうちの少なくとも2.2%で原診断と再検討診断の間に深刻な不一致が生じていることが明らかとなった。がん診療に不可欠な病理診断に関する情報伝達の確度を確保し適切な治療を施行するために、紹介元施設は原診断書や診断に使用された病理標本（または未染色標本）を確実に送付し、紹介先施設では原診断書をカルテ上で閲覧可能とし病理診断の再検討を施行することが重要であると考える。

F. 研究発表

なし

G. 知的財産権の出願・登録状況

1. 実用新案登録

なし

2. その他

なし

3. 特許取得

なし

厚生労働省科学研究費補助金（がん臨床研究事業）
分担研究報告書書

日本の主要新聞における臨床試験に関する報道の傾向に関する研究

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研究要旨
背景：新聞は、国民に臨床試験に関する情報を伝えるための有効な手段である。しかしながら、新聞における臨床試験に関する報道の実態は分かっていない
方法：日本における最大の新聞データベース（日経テレコン21）を用い、1992年から2007年の主要5紙に掲載された総記事数、臨床試験や臨床試験に関連するキーワードについての記事数の年次推移を調査した。
結果：総記事数は1992年は約560,000件で、2001年には約1,300,000件となり、以後横ばいであった。総記事に占める"臨床試験"関連記事の割合は、薬害事件が社会問題となった1996年に0.17%に増加した以外は、約0.07%で変わらなかった。2000年以降、経済専門紙である日経新聞は臨床試験に関する記事数が増加したが、その大部分は新薬開発など製薬企業の業績と関連していた。一方、日経以外の4紙の記事数は横ばいであった。各種キーワードの検索数の総記事数に対する割合は、1994年に臨床試験相の方法（Phase, Protocol）に関連した記事、1996年に厚労省、訴訟、薬事法、治験、倫理などの行政や法律に関連した記事がピークを迎えていた。
結論：本研究は、臨床試験が主要新聞の報道対象であることを示した。しかしながら、多くの新聞は、製薬企業の業績や薬害事件など不祥事に重点をおき、これらとの関連で臨床試験の情報を報道している。

A. 研究目的

新規薬剤や治療法を開発するためには臨床試験が必要である。臨床試験を円滑に遂行するためには、一般市民の臨床試験に関するリテラシー向上が欠かせない。このためには、臨床試験に関する情報が公開され、国民に理解可能な形で提供されなければならない。しかしながら、厚生労働省研究班調査によれば、一般患者の5割で、治験参加者の7割で治験に関する情報は不足していると回答しているように、国民は臨床試験に関する情報提供は不十分と感じている。

新聞やテレビなどのマスメディアは国民に情報を伝える有効な手段である。テレビの視聴率8.3%は約300万人に相当し（2）、主要新聞の部数は220万から1,000万部にも上る。このように、マスメディアを用いれば、多数の国民に一斉に情報を伝達することが出来る。逆に、国民の医療に関するリテラシーの向上のためには、マスメディアの協力が必須である（3-5）。しかしながら、多くの医師はマスメディアの医療報道に不満を抱いており（2）、両者の関係は良好とは言えない。

臨床試験の効率的な遂行のためには、マスメディアの協力が必須である。しかしながら、マスメディアでの臨床試験についての報道を体系的に調査した研究はなく、その実態は不明である。我々は、最新の新聞データベースを用い、

主要新聞における臨床試験に関連する報道の実態を調査した。

B. 研究方法

我が国における五大主要紙（朝日新聞、毎日新聞、読売新聞、産経新聞、日本経済新聞）を対象とした。これらの新聞の一日あたりの購読者数は合計2,700万人である。

日本で最も大きい新聞データベースである日経テレコンを用い、記事情報を抽出した。このデータベースは、日本で発行されている殆どの新聞をしてカバーおり、主要五大紙については、1992年以降の記事は網羅できている。

まず、医学中央雑誌のシソーラス検索を用いて、「臨床試験」の関連語を抽出し、次の単語をキーワードと定義した。; investigational agent, preclinical study, drug screening, nonclinical test, clinical trial, sponsored study, clinical protocol, prospective study, comparative test, blind study, phase I study, phase II study, phase III study, phase IV study, post-marketing surveillance, randomized clinical trial, Good Clinical Practice, Good Laboratory Practice, clinical research coordinator, Institutional Review Board, clinical investigator. その後、前述の記事を対象に、これらのキーワードが含まれる記事の数、年次推移、およびその内容を調査した。

1992年から2007年までの間に、我が国の主要五大紙で配信された臨床試験に関連した新聞記事の数、およびその報道内容を調査することを目的とする。

C. 研究結果

五大主要紙の記事数の推移をFigure1Aに示す。記事数は1990年代初頭から増加したが、2000年以降はほぼ一定である。2000年以降、読売、朝日、毎日新聞の記事数は日経、産経新聞の約3倍である。

五大主要紙における臨床試験関連記事数の推移をFigure1Bに示す。全記事に対する臨床試験関連記事数の割合は、五大紙全てが1996年に0.167%と一過性に上昇している。その後、日経新聞は2000年以降に記事数が増加し、産経新聞は2002年に小さなピークを迎えていた。日経新聞の記事の大部分は、新薬開発など製薬企業の業績と関連していた。日経新聞以外の4紙では、他の時期の記事数の割合は0.07%前後で一定であった。

各キーワードの出現がピークとなった年をFigure 3に示す。主たるキーワードは、1994年と1996年に二つのピークを有する。1994年はPhaseやProtocolなどの臨床試験の方法論に関する単語がピークを迎え、1996年には厚労省、訴訟、薬事法、治験、倫理などの単語がピークであった。

D. 考察

本研究は、新聞報道において、臨床試験が一定のスペースを占めていることを示した。主要五大紙における臨床試験関連の記事の比率は約0.07%であり、1日あたり2-3の記事が配信されている。高齢化の進展とともに、国民の医療への関心は高まっているため、多くの臨床医は主要新聞における臨床試験の報道数も増加していると感じている。しかしながら、このような予想に反し、日経新聞を除く4紙では、1996年の一過性のピークを除き、記事の比率はほぼ一定である。つまり、医療界の努力にもかかわらず、一般紙における臨床試験の取り扱いは増加していない。多くの国民は、新聞から医療に関する情報を入手することを考慮すれば、近年、国民の臨床試験に関するリテラシーが大きく向上したとは考えにくい。

臨床試験の記事の比率は新聞社によって大きな差を認めた。特に、近年、日経新聞における臨床試験関連の記事の比率が増加していることは興味深い。2002年以降の臨床試験の記事の比率は1990年代の倍以上である。日経

新聞は経済専門誌であり、製薬企業を我が国の成長分野と見なし、臨床試験を製薬産業の投資や業績という視点から報道している。多くの医療者は臨床試験を投資や経済成長の視点から見ることは少なく、国民の視点との間に乖離が存在するかもしれない。

臨床試験関連の記事は1996年に急増している。これは、同年に薬害エイズ事件や薬害ヤコブ病事件が社会的話題になったためである。また、1994年にはソリブジン治験に関する不祥事が社会問題化し、記事数が増加している。このような事実は、マスメディアは事件や新規性のある事象を好んで取り扱うことと合致する。1994年、および1996年には、「厚労省」、「訴訟」、「薬事法」、「治験」、「倫理」や「Phase II」や「Phase III」などの治験の方法に関するキーワードの出現頻度が増えていた。このため、国民は薬害事件や治験に関する不祥事の報道を通じて、臨床試験の方法論や薬事行政のあり方に関する情報に接したと考えられる。主要新聞で、臨床試験が薬害事件や不祥事と関連して報道されることは、臨床試験に対する国民の心証形成に負の影響を与えている可能性が否定できない。

一方、我が国では2000年代に入り、臨床試験の体制整備が進み、2002年には薬事法が大きく改正された。本研究でも、2002年に「Coordinator」、2005年に「医師主導治験」というキーワードがピークを迎えている。この時期には大きな薬害や不祥事はなく、このようなキーワードは臨床試験の制度改正の記事で用いられていた。ここで注意すべきは、「Coordinator」や「医師主導治験」に関する報道量は、1996年の薬害報道の10%程度ということである。この事実は、薬事行政や臨床試験の制度論について、新聞で報道することはあっても、その報道量は多くないことを意味している。このため、薬害や不祥事と比較して、臨床試験の制度改革は、国民への理解が進みにくいのかもしれない。このような事実を考慮すれば、臨床試験に対する国民の理解を深めるためには、事件や不祥事に重点を置くことが多い新聞以外の情報提供手段が必要なのかもしれない。

E. 結論

本研究は、臨床試験が主要新聞の報道対象であることを示した。しかしながら、多くの新聞報道は、製薬企業の業績や薬害事件など不祥事に重点をおき、臨床試験の制度については十分な情報を提供していない。医療者は、主要新聞のこのような特性について十分に理解すべきである。

F. 研究発表

1. 論文発表

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2. Morita T, Hori A, Narimatsu H, Tanimoto T, Kami M. Current status of development of anticancer agents in Japan. International Journal of Hematology. 87:484-489, 2008.

2. 学会発表

なし

G. 知的財産権の出願・登録状況（予定を含む。）

なし

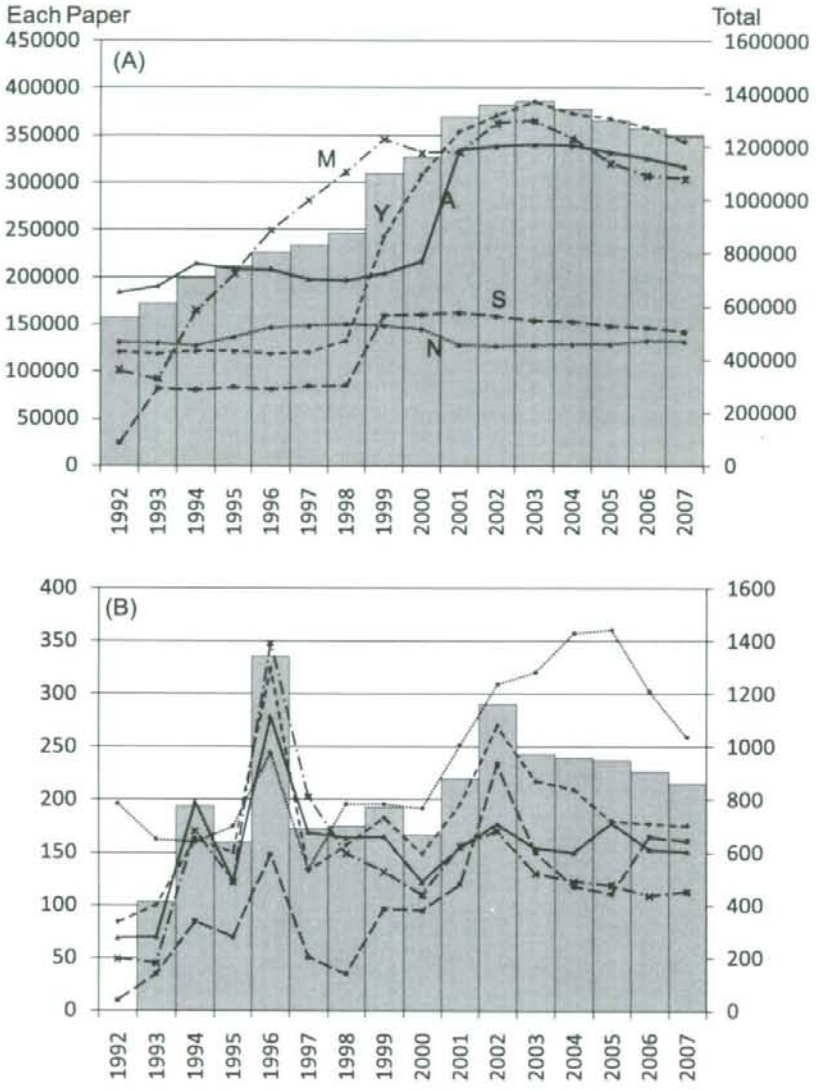

Figure 1: 主要新聞紙における記事数

(A) 五大新聞紙における総記事数; (B) 五大新聞紙における臨床試験に関する記事数

A: 朝日新聞, M: 毎日新聞, Y: 読売新聞, S: 産経新聞, N: 日本経済新聞, 棒グラフは5大紙の総合計を示す。

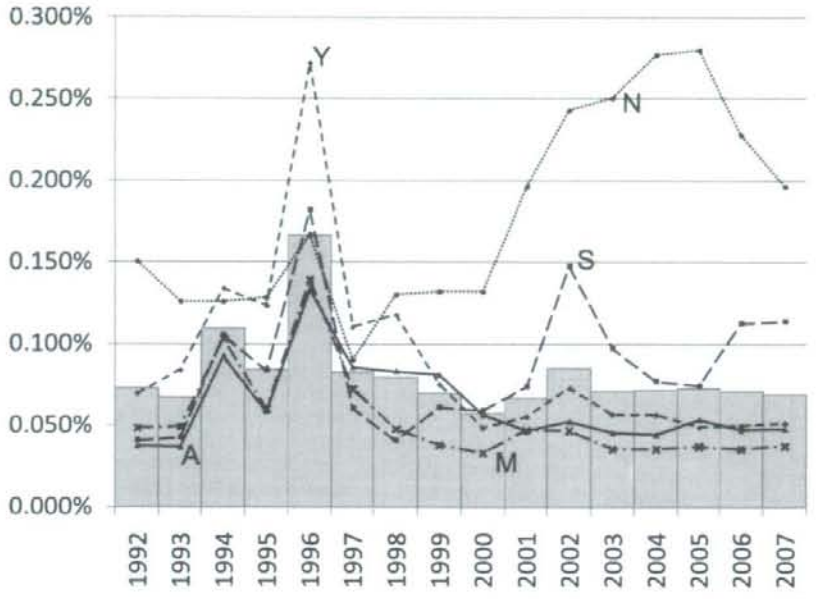

Figure 2: 臨床試験に関連した記事の全記事数に対する割合
A: 朝日新聞, M: 毎日新聞, Y: 読売新聞, S: 産経新聞, N: 日本経済新聞, 棒グラフは5大紙の総合計を示す。

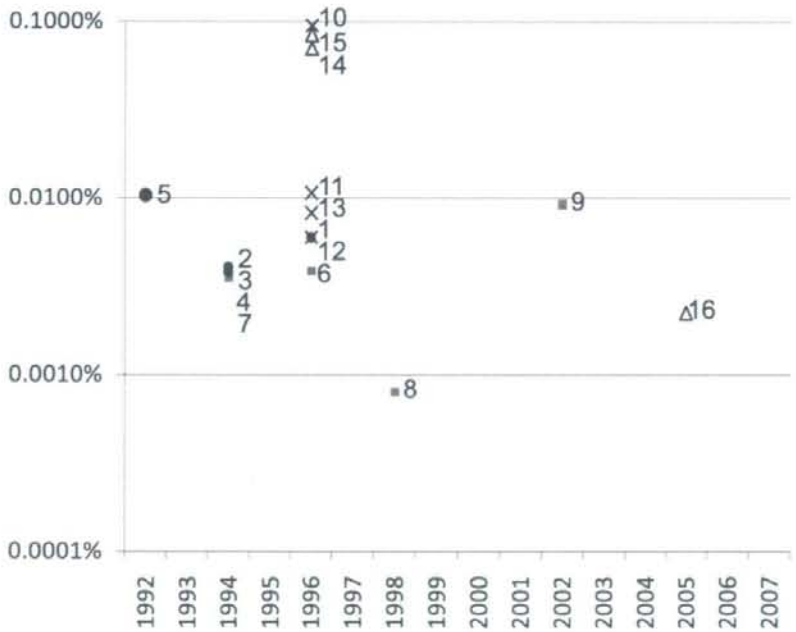

Figure 3: キーワード別記事割合とそのピーク年
●:「相」関連語, ■: 手続き・制度関連語, ×: 政治・行政関連語, △: その他
1. phase I study, 2. phase II study, 3. phase III study, 4. phase IV study, 5. preclinical test, 6. Randomization, 7. Protocol, 8. Good Clinical Practice, 9. Coordinator, 10. Ministry of Health, Labour and Welfare, 11. Pharmaceutical Affairs Law, 12. Guideline, 13. Ethics, 14. investigational drug, 15. Lawsuit, 16. Doctor-led model clinical trials

Ⅲ．研究成果の刊行に関する一覧

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takita M, Tanaka Y, Hamaki T, Matsumura T, Narimatsu H, Kishi Y, Kodama Y, Nishimura T, Goto T, Nagai M, Kami M.	Regional social system for specialized medical care in hematologic malignancies: a pilot study.	Rural and Remote Health			in press
Takita M, Narimatsu H, Matsumura T, Kishi Y, Murashige N, Hamaki T, Kodama Y, Yuji K, Tanaka Y, Kami M.	A Study of Newspaper Reports Regarding Clinical Trials in Japan.	Journal of Clinical Oncology			in press
Miura Y, Yamaguchi T, Azuma T, Hamaki T, Kodama Y, Kusumi E, Matsumura T, Nakamura T, Kami M, Komatsu T.	Regional differences exist in allogeneic stem cell transplantation rates for acute leukemia.	International Journal of Hematology	87	236-238	2008
Morita T, Hori A, Narimatsu H, Tanimoto T, Kami M.	Current status of development of anticancer agents in Japan.	International Journal of Hematology	87	484-489	2008

Ⅳ．研究成果の刊行物、別刷り

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LETTER TO THE EDITOR

Regional differences exist in allogeneic stem cell transplantation rates for acute leukemia

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Allogeneic stem-cell transplantation (allo-SCT) is a curative treatment for advanced hematologic malignancies, although it is frequently accompanied by severe complications and the practice is usually limited to experienced medical teams [1]. Regional differences in indications and management strategies for allo-SCT among physicians and institutions have been indicated; however, their existence and factors associated with them among physicians and institutions remain unknown. We examined the differences in allo-SCT rates for acute leukemia among prefectures and districts in Japan, and investigated the association between the differences and several possible factors. Japan's prefectures comprise the 47 administrative units of the country, and districts make up ten areas divided according to geographical and historical backgrounds: Hokkaido, Tohoku, Koshinetsu, Kanto, Tokai, Hokuriku, Kinki, Chugoku, Shikoku, and Kyushu.

Since 97% of the patients who underwent allo-SCT for acute leukemia from 2000 to 2004 were younger than 60 years in Japan [2], we assumed that allo-SCT was indicated in patients aged less than 60. We defined allo-SCT rates as the rate of the number of patients who underwent allo-SCT to that of patients with acute leukemia. We investigated the number of patients with acute leukemia aged less than 60 as a denominator and the number of those who underwent allo-SCT under the age of 60 as a numerator. We estimated the annual number of new patients with acute leukemia under the age of 60 in each prefecture and district, using the incidences of acute leukemia by age-groups in Japan [3] and the population by age-groups in each prefecture according to a census in 2004 [4]. We defined the number of treated patients in each district as the estimated number of patients with acute leukemia, while the number of patients in each prefecture was adjusted by patient migration to and from other prefectures [5]. The number of patients who underwent allo-SCT for acute leukemia under the age of 60 in each prefecture and district from 2000 to 2004 was obtained from the annual report in 2005 published by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) [2]. We assumed the percentage of acute leukemia to the primary diseases for which allo-SCT was indicated in each prefecture to be the same as the national average (83%) during the same time period [2], because JSHCT reports the total numbers of the primary diseases for which allo-SCT was indicated in Japan without the breakdown of data by prefecture. We investigated the association between the differences and several possible factors using the Spearman correlation coefficient (significance level 0.05). They included physicians per unit population [6], the numbers of

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hematologists per unit population [7], the numbers of allo-SCT institutions per unit population [2], and incomes per person [8] in prefectures and districts.

The estimated number of patients who developed acute leukemia under the age of 60 years from 2000 to 2004 in Japan was 3,075 per year. The number of patients who underwent allo-SCT for acute leukemia under the age of 60 during this period was 1,633 per year. The allo-SCT rate in Japan was 53%.

The allo-SCT rates by district were high in the west and low in the east (Fig. 1a), with a maximum 2.1-fold difference (31 vs. 65%) [95% confidence interval (CI): 1.9 to 2.4-fold]. There was a trend between the allo-SCT rates by district and the numbers of hematologists per unit population ($r = 0.5627$, $P = 0.0963$), while no association was found between the numbers of physicians per unit population ($r = 0.4012$, $P = 0.2475$), allo-SCT institutions per unit population ($r = 0.4233$, $P = 0.2182$), or incomes per person ($r = 0.1255$, $P = 0.7298$).

The allo-SCT rates by prefecture are shown in Fig. 1. There was a maximum 17.9-fold difference (5.6 vs. 100%) (95% CI 11.0 to 29.3-fold). No prefectures in Tohoku or Koshinetsu districts had allo-SCT rates exceeding 60%. The allo-SCT rates by prefecture were significantly associated with the numbers of physicians, hematologists, and allo-SCT institutions per unit population [$r = 0.4354$ ($P = 0.0022$), $r = 0.5773$ ($P < 0.0001$), $r = 0.5255$ ($P = 0.0001$)]; these three factors were significantly associated with each other. There was no association between the allo-SCT rates by prefecture and incomes per person ($r = 0.1147$, $P = 0.4426$). The year of the foundation of medical faculties in each prefecture was associated with the allo-SCT rates (Fig. 2).

The present study demonstrated that the allo-SCT rates for acute leukemia were different among districts in Japan, with a maximum 2.1-fold difference. The results were comparable with previous reports from Europe; Gratwohl et al. [9] reported a maximum 2.8-fold difference in the numbers of allo-SCT per unit population in Western Europe. However, we need to be aware of differences in the backgrounds, when our study is compared with the report by Gratwohl et al. Their study on allo-SCT activities in different countries in Western Europe with varying medical administrative systems sharply contrasts to ours based on a single country managed by a single administrative system. Since each district constitutes an independent medical service area with negligible patient migration among districts in Japan [5], the present study suggests that factors other than administrative systems affect the difference in allo-SCT activities among districts. Identifying these factors and taking countermeasures are important for the spread of allo-SCT.

Our study suggested that the number of hematologists per unit population possibly affects the allo-SCT rates by district. This observation implies that education to increase the number of physicians who can manage allo-SCT is necessary for its dissemination. As education to increase numbers of physicians is limited to medical faculties at

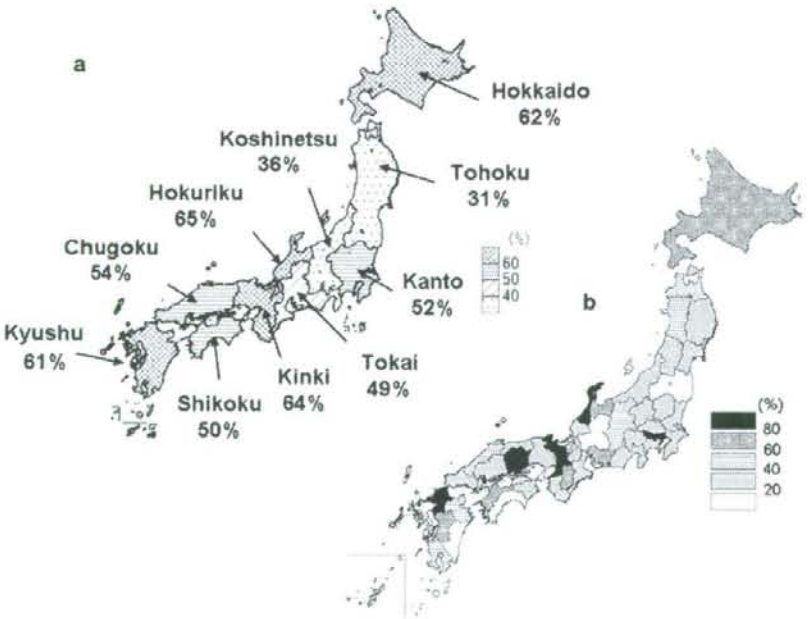

Fig. 1 **a** Allogeneic stem cell transplantation rates by district, **b** allogeneic stem cell transplantation rates by prefecture. The allogeneic stem cell transplantation rates were 62% in Hokkaido, 31% in Tohoku, 36% in Koshinetsu, 52% in Kanto, 49% in Tokai, 65% in Hokuriku, 64% in Kinki, 54% in Chugoku, 50% in Shikoku, and 61% in Kyushu

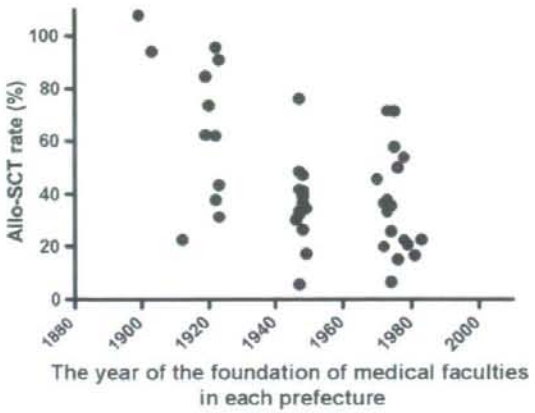

Fig. 2 Association of allogeneic stem cell transplantation rates by prefecture with the year of the foundation of medical faculties in each prefecture

universities and colleges in Japan, the number of physicians in a district is probably affected by the regulated number of students at medical faculties and the year of the foundation of medical faculties. The present study showed a significant association between the year of the foundation of medical faculties in each prefecture and the allo-SCT rates (Fig. 2). The allo-SCT rates by district which were high in the west and low in the east are probably explained by the history where medical faculties had been founded mostly in Western Japan since the Meiji Revolution in 1868. Depending on the migration of health care professionals seems insufficient to minimize the difference in medical services; focusing on the first step of physicians' education will be important. The present study also demonstrated no significant association between incomes per person and the allo-SCT rates by district. The national health insurance system which reduced the economical difference in access can explain the negative results in association between economical factors and the allo-SCT rates in Japan.

The present study showed a maximum 14.6-fold difference in allo-SCT rates among prefectures in a single district. The observation suggests that a prefecture plays a central role in each district and that patients cross the prefectural border to the central prefecture to undergo allo-SCT. Interestingly, no central prefecture exists in Tohoku district, where the allo-SCT rate was the lowest. Since the Japanese capital had been located in Kinki district (West Japan) until the mid nineteenth century, mainly West Japan was developed. The weak economical platform and premature social infrastructure in East compared with West Japan may hamper the centralization of allo-SCT in Tohoku.

Our study has some limitations. While we used relatively accurate numbers of allo-SCT, we could not obtain actual data on the incidences of acute leukemia in prefectures and patient migration rates to and from other prefectures. We estimated the former based on incidences by age-groups and populations, and adjusted the latter with the rates of immigration and emigration of all patients, yet the allo-SCT rates reached 100% in some prefectures. The results suggest that patients with acute leukemia more often cross the prefectural border for allo-SCT than for regular treatments. Data collection by the registration of patients with acute leukemia and the further investigation of patient migration for allo-SCT are warranted.

In conclusion, the present study suggested that social systems including physicians' education largely affect the dissemination of complex medical treatments such as allo-SCT. To reduce the regional differences in allo-SCT by the centralization of allo-SCT institutes, improvement of the education system for physicians and social infrastructure also needs to be considered.

Acknowledgments The present research was funded by Health Labour Sciences Research Grant by the Ministry of Health, Labour and Welfare, Japan.

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ORIGINAL ARTICLE

Current status of development of anticancer agents in Japan

Tomohiro Morita · Akiko Hori · Hiroto Narimatatsu · Tetsuya Tanimoto · Masahiro Kami

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Abstract To investigate the current status of the development of anticancer agents in Japan, we examined the number of these agents developed after 1999, their target diseases, and the association between the number of approved agents and the number of patients with the diseases. The data were obtained via the Internet. Of the 487 agents approved from 1999 to April 2007, 84 were anticancer drugs. Of these 84, 46 were approved based on clinical trials and 38 were approved through the new drug application for off-label usages without clinical trials. The target diseases of the 46 agents approved through clinical trials were nonhematologic tumors in 29, hematologic malignancies in 13, and others in 4. Of the 38 approved through the new drug application for off-label usages, 31 were for nonhematologic tumors and 7 for hematologic malignancies. The number of approved anticancer agents for hematologic malignancies per unit patient population was 6.5-times as many as that for nonhematologic tumors. This study demonstrated that the situation regarding the development of anticancer agents differs among tumor types. The majority of anticancer agents developed target hematologic malignancies, while the newly developed anticancer agents have affected treatment strategies for solid tumors.

Keywords Approval · Cancer · PMDA · Off-label use

1 Introduction

The number of cancer patients is increasing with rapid population aging in Japan [1]. Despite the progress of medical technology, the prognosis of cancer remains insufficient. When cure or prolongation of survival cannot be expected through existing surgery and chemotherapy, patients strongly desire to be involved in trials of novel anticancer agents. Since anticancer agents with novel mechanisms such as molecular targeting agents and antibody drugs were developed, the development of chemotherapeutic agents for cancers which have not responded to conventional cytotoxic agents has been attempted [2]. The number of newly developed anticancer agents is, therefore, increasing [3].

The so-called drug-lag, the delay in the availability of drugs in Japan which are already available in Europe and/or the US, is a social concern in Japan [4]. One of the reasons that Japan lags behind Europe and the US in the approval of anticancer agents is that development by drug manufacturers in Europe and/or the US precedes that in Japan [4]. The Ministry of Health, Labour and Welfare initiated discussions at the Conference on Unapproved Drug Use in January 2005 to reduce this drug-lag. The Ministry requests drug manufacturers to rapidly complete clinical trials in Japan on drugs which are judged necessary by the conference. As of April 2007, the conference deals with 35 agents (ingredients), of which 21 are anticancer agents [5].

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Hematologic malignancies have been the major target of developed anticancer agents, despite their low incidence. This is related to the easy access to tumor samples and the high response rates to anticancer agents compared with solid tumors. The development of molecular targeting agents and antibody drugs and the social changes in cancer treatment have led to advances in the development of novel anticancer agents for solid tumors; however, the actual condition remains unclear. We investigated the number of anticancer agents which were developed after 1999, the target diseases, and the association between the number of approved anticancer agents and the number of patients with the diseases.

2 Materials and methods

2.1 Definition of anticancer agents

We defined anticancer agents as drugs used for antitumor activities and excluded supportive treatments and drugs used for complications or adverse effects of treatments such as bisphosphonates. We defined molecular targeting agents as drugs which aim at the selective inhibition of the transformed phenotype or target specific molecular lesions within tumor cells, leading to improved cure rates with limited toxicity.

2.2 Information collection regarding approved anticancer agents

The generic names, effects, and year of approval of anticancer agents which were approved from 1999 to April 2007 were obtained from the homepages of the Pharmaceuticals and Medical Devices Agency (PMDA) [3] and Japan Pharmacists Education Center (JPEC) [6]. When an identical chemotherapeutic agent was approved for another use, we treated it as a separate agent.

2.3 Information collection regarding anticancer agents undergoing development

While information on anticancer agents undergoing development in order to apply for approval is not publicly available, the agents which were judged necessary for early development or approval application by the Conference on Unapproved Drug Use are listed in "Information on unapproved drugs in Japan [7]" on the homepage of the Cancer Information Center at the National Cancer Center. In the present study, we considered the agents listed on the homepage as of 15 April 2007 as the drugs which were in preparation for approval application in Japan and collected information on the generic names and expected target diseases of those agents.

2.4 Information collection regarding the number of cancer patients

Incidence data were obtained from the homepage of the Cancer Information Center at the National Cancer Center [8] and the numbers of patients with different tumors were estimated. The investigated tumors were classified into brain tumor, head and neck, esophageal, gastric, colorectal, breast, uterine, ovarian, prostate, renal, bladder, hepatic, biliary tract, pancreatic, skin, and lung cancers as well as other solid tumors, malignant lymphoma, leukemia, other hematologic malignancies, and others.

2.5 Objectives

The primary objective of the present study was to clarify the numbers of anticancer agents which were approved from 1999 to April 2007, developing agents as of April 2007, and the target diseases. The secondary objective was to investigate the method of approval of each drug and to evaluate the association between the number of approved anticancer agents and the number of patients with the diseases.

3 Results

3.1 Approved anticancer agents

Of 487 applications approved from 1999 to April 2007, 84 (17%) were anticancer agents. Of these 84, 46 were approved based on the data obtained from clinical trials for approval, and 38 were approved based on the new drug application for off-label usages without clinical trials in Japan. The annual numbers of approved applications for anticancer agents are shown in Fig. 1. The number of approved applications increased in 2005, when the administrative measures approved 25 applications for anticancer agents, which had been used off-label.

The target diseases regarding the 46 applications of anticancer agents approved based on clinical trials in Japan were nonhematologic tumors in 2, hematologic malignancies in 13, and others in 4. These four agents categorized in others were all related to preparative regimens for hematopoietic stem cell transplantation. Details of the approved applications are shown in Table 1. No agents were approved for ovarian, renal, bladder, and skin cancer. Of the 46 applications, 10 were molecular targeting agents, and 7 of them targeted hematologic malignancies. The Conference on Unapproved Drug Use was involved in four applications (pemetrexed disodium, bortezomib, temozolomide, and oxaliplatin).

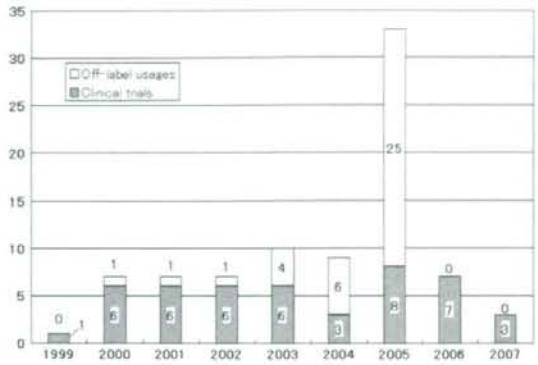

Fig. 1 Number of anticancer agents approved through clinical trials or approved based on the new drug application for off-label usages between January 1999 and April 2007. The number of approved anticancer agents varied from 1 to 10 during the study periods except for 2003. The Conference on Unapproved Drug Use was held in 2003, and 25 anticancer agents were approved based on the new drug application for off-label usages

Of 29 applications of anticancer agents for solid tumors for which approval was applied for approval by a regular method, 8 (pemetrexed disodium, cisplatin, temozolomide, oxaliplatin, gefitinib, imatinib mesilate, trastuzumab, and gemcitabine hydrochloride) and 2 (pemetrexed disodium and cisplatin) underwent priority and accelerated reviews, respectively. Of the eight applications, three were qualified as orphan drugs (imatinib mesilate, trastuzumab, and gemcitabine hydrochloride). Of 13 applications regarding anticancer agents for hematologic malignancies, 9 applications underwent priority review (arsenic trioxide, bortezomib, gemtuzumab ozogamicin, tamibarotene, rituximab, cladribine, imatinib mesilate, cytarabine, and fludarabine). Eight of them were qualified as orphan drugs (bortezomib, gemtuzumab ozogamicin, tamibarotene, rituximab, cladribine, imatinib mesilate, cytarabine, and fludarabine). The four applications classified into others which were related to conditioning regimens for hematopoietic stem cell transplantation were all qualified as orphan drugs.

Of the 38 applications of anticancer agents approved through new drug application for off-label usages, 31 were for nonhematologic tumors and 7 for hematologic malignancies. The names of these agents were: doxorubicin hydrochloride, vincristine sulfate, dexamethasone sodium phosphate, cisplatin, methylprednisolone succinate, cytarabine, and dacarbazine. The additional usages of these seven agents included VAD therapy for multiple myeloma, DHAP and ESHAP therapy for malignant lymphoma, high-dose cytosine arabinoside therapy for leukemia and lymphoma, and ABVD therapy for Hodgkin's disease. The target diseases are shown in Table 1. Molecular targeting agents were not included in the 38 applications. No agents were discussed in the Conference on Unapproved Drug Use.

3.2 Anticancer agents during development

As of April 2007, there were 20 anticancer agents in preparation for approval application in Japan: erlotinib for lung cancer, streptozocin for pancreatic cancer, sunitinib for gastrointestinal stromal tumor and kidney cancer, cetuximab for colorectal cancer, sorafenib for kidney cancer, doxorubicin hydrochloride for ovary cancer, bevacizumab for colorectal cancer, alemtuzumab for leukemia, yttrium Y 90 ibritumomab tiuxetan for lymphoma, clofarabine for leukemia, thalidomide for multiple myeloma, dasatinib for leukemia (myeloid and lymphoid), decitabine for myelodysplastic syndrome, iodine I 131 tositumomab for lymphoma, nelarabine for leukemia and lymphoma, pegaspargase for leukemia, and lenalidomide for myelodysplastic syndrome. Target diseases included hematologic malignancies in 12 and solid tumors in 8. Of the 20 applications, 11 were molecular targeting agents, and 5 of them targeted hematologic malignancies.

Of the 20 agents undergoing development, 16 were in clinical trials in Japan and the remaining 4 were in preparation for applying for approval through new drug application for off-label usages. All 20 agents were discussed in the Conference on Unapproved Drug Use.

3.3 Association between the number of anticancer agents and the number of patients with the diseases

The estimated numbers of patients with different tumors in Japan are shown in Table 1. Detailed information on the numbers of applications approved through clinical trials, approved through new drug application for off-label usages, and during development per 100,000 patients according to the types of malignancies is shown in Table 1.

Concerning the 84 chemotherapeutic applications approved from 1999 to April 2007, 79 agents per 100,000 patients with hematologic malignancies and 12 per 100,000 patients with nonhematologic malignancies were approved.

4 Discussion

The present study demonstrated that the situation regarding the development of anticancer agents differs among tumor types. Given the news on the approval of bevacizumab [9], and oxaliplatin for colorectal cancer in Japan [10], and the development of sorafenib for hepatic cancer [11] and erlotinib for non-small cell lung cancer [12] in Europe and the US, many clinicians recently feel that the development

Table 1 Number of anticancer agents, target diseases, and patients with the diseases

	Types of malignancy	Number of cancer patients	Approved drugs						During development	
			Clinical trial		Off-label usages		Total			
			Number of agents	Per 100,000 patients	Number of agents	Per 100,000 patients	Number of agents	Per 100,000 patients	Number of agents	Per 100,000 patients
Non-hematologic	Brain	4,392	1	22.8	2	45.5	3	68.3	0	0.0
	Head and neck	12,934	1	7.7	1	7.7	2	15.5	0	0.0
	Esophagus	15,451	1	6.5	0	0.0	1	6.5	0	0.0
	Stomach	102,785	1	1.0	0	0.0	1	1.0	0	0.0
	Colon and rectum	92,137	2	2.2	1	1.1	3	3.3	2	2.2
	Breast	37,389	8	21.4	4	10.7	12	32.1	0	0.0
	Uterus	19,812	3	15.1	2	10.1	5	25.2	0	0.0
	Ovary	7,490	0	0.0	0	0.0	0	0.0	1	13.4
	Prostate	19,825	2	10.1	0	0.0	2	10.1	0	0.0
	Kidney	10,837	0	0.0	0	0.0	0	0.0	2	18.5
	Bladder	13,700	0	0.0	4	29.2	4	29.2	0	0.0
	Liver	40,053	1	2.5	1	2.5	2	5.0	0	0.0
	Gallbladder and Bile duct	17,238	1	5.8	0	0.0	1	5.8	0	0.0
	Pancreas	20,045	2	10.0	0	0.0	2	10.0	1	5.0
	Skin	6,859	0	0.0	0	0.0	0	0.0	0	0.0
	Lung	67,890	3	4.4	1	1.5	4	5.9	1	1.5
	Other solid	7,888	3	NA	15	NA	18	NA	1	NA
	Total	496,725	29	5.8	31	6.2	60	12.1	8	1.6
Hematologic	Lymphoma	13,307	4	30.1	4	30.1	8.0	60.1	3	23.0
	Leukemia	7,888	8	101.4	0	0.0	8.0	101.4	6	76.0
	Other hematologic	4,120	1	NA	3	NA	4	NA	3	NA
	Total	25,315	13	51.4	7	27.7	20	79.0	12	47.4
	Others	134,659	4	NA	0	NA	4	NA	0	NA
	Total	656,699	46	7.0	38	5.8	84	12.8	20	3.0

NA not applicable

of anticancer agents for solid tumors has progressed. Indeed, the agents have affected the treatment strategies of solid tumors; however, the present study showed that 24% (20/84) of approved drugs and 60% (12/20) of unapproved drugs are for hematologic malignancies, suggesting that the majority of development of anticancer agents still targets hematologic malignancies. The incidences of gastric, colorectal, lung, hepatic, and breast cancers are high in Japan, constituting 52% of all cancer patients, while the estimated annual number of patients with hematologic malignancies is 25,315 (3.9%). The number of approved and unapproved anticancer agents for hematologic malignancies per unit patient population was 9.2-times as many as that for nonhematologic tumors. As the prognosis of relapsed and/or advanced solid tumors remains poor, the treatment methods for solid tumors have not sufficiently developed and thus require further investigations.

Some possibilities exist to explain our results, whereby the development of anticancer agents mostly targets hematologic malignancies rather than solid tumors. First, hematologic malignancies are highly sensitive to anticancer agents [13]. This is consistent with our observation that many agents have been developed for breast cancer, which has a relatively high sensitivity to anticancer agents compared with other solid tumors. Second, different administrative processes involved in the investigation for approval may have an influence. In Japan, drugs which target few patients without other effective treatments and are likely to show effectiveness are qualified as orphan drugs [14], and drugs for life-threatening diseases which show good results in terms of effectiveness and safety undergo priority and accelerated reviews [15]. The present study demonstrated that drugs for hematologic malignancies are more likely to be qualified as orphan drugs than those for nonhematologic tumors, suggesting the possibility that drugs for hematologic malignancies undergo favorable administrative processes. Such an administrative system may promote the development of anticancer agents for hematologic malignancies by pharmaceutical companies.

The present study demonstrated that both the approval process based on clinical trials in Japan and that through new drug application for off-label usages without clinical trials play important roles in the Japanese system for the approval of anticancer agents. Of the 84 applications approved from 1999 to April 2007, 46 (55%) underwent the former and 38 (45%) the latter. The former mostly aimed at the introduction of novel anticancer agents to clinical use in Japan which had been developed in Japan or abroad, and the latter mostly aimed at adding new indications or administrative measure to agents which had already been approved for other diseases. While 13 of the 46 applications approved based on clinical trials were for hematologic malignancies, 7 of the 38 agents approved through new drug application for off-label usages were also for hematologic malignancies. The approval process through new drug application for off-label usages is more often utilized in agents for nonhematologic tumors than in those for hematologic malignancies; off-label use may more often become an issue in solid tumors than in hematologic malignancies. In the future, research from the viewpoint of drug-lag is expected to reveal characteristic differences in the development of antitumor agents between Japan and foreign countries.

The present study demonstrated that the Conference on Combination Chemotherapy and Conference on Unapproved Drug Use held by the Ministry of Health, Labour and Welfare played certain roles in the development of anticancer agents in Japan. Notably, 28 applications for anticancer agents were approved in 2005 to resolve the problem of off-label drug use after discussion at the Conference on Combination Chemotherapy, and Conference on Unapproved Drug Use discussed 20 novel chemotherapeutic compounds approved during research periods. The former is considered to have contributed to bridging the inevitable gap [4, 16] in the Japanese health care system between approval based on pharmaceutical law and approval for the national health care insurance; however, nationwide discussion is necessary on the levels of administrative burden in clinical trials and new drug application for off-label usages that are required to resolve the problems of off-label drug use [17, 18]. Most of the anticancer agents, to which newly approved indications were added, have been used off-label without problems [19], and the rush for new drug applications for off-label usages, greatly burdening the PMDA, has possibly delayed the approval of novel anticancer agents [4]. In contrast, the role of the latter, the Conference on Unapproved Drug Use, awaits further investigation. Drug manufacturers make decisions on drug development based on general information, including cost management. Although the recommendations made by the Conference on Unapproved Drug Use are highly likely to have urged drug makers to introduce novel anticancer agents developed abroad to the Japanese market, such drugs may not have been developed in Japan without administrative intervention. The negative aspects of administrative intervention need to be studied.

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