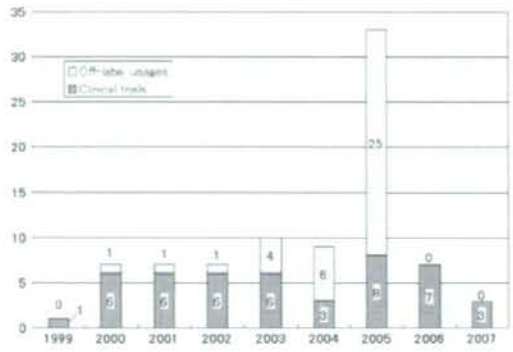

Fig. 1 Number of anticancer agents approved through clinical trials or approved based on the new drug application for off-label usages between January 1999 and April 2007. The number of approved anticancer agents varied from 1 to 10 during the study periods except for 2003. The Conference on Unapproved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

とくしまの くらし しっかり まもってる

全国どこにいても同じ水準のがん医療が受けられる「均てん化」というものが、国によって推進されていること、ご存じでしょうか。水準をそろえるためには、地域によってどの程度のバラツキがあるか調べることが必要です。そこで、私たちは今回、徳島県内について、医療体制がどの程度充実しているか、高度医療が必要とするがん患者さんに行き渡っているか調べてみました。悩む患者さんも多くなる結果が出ました。

例えば、がんの患者さんの場合で見てみると…

白血病、悪性リンパ腫、多発性骨髄腫に罹っている患者さん

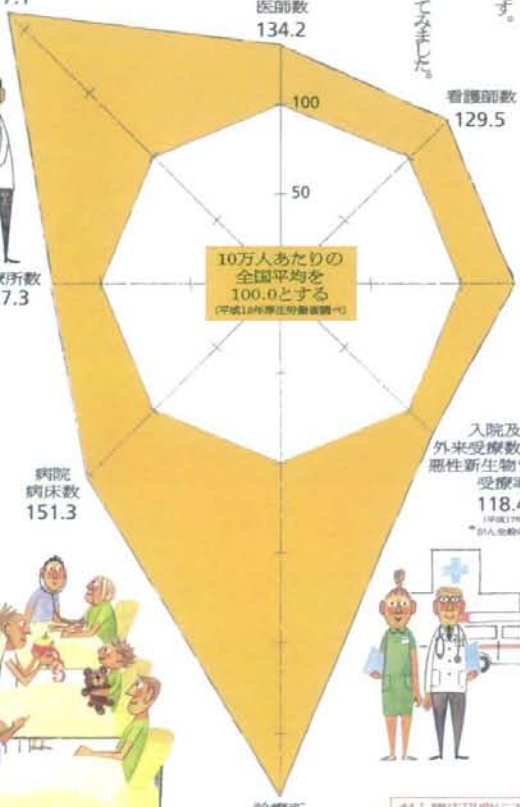
1. どのくらいの患者さんがいますか?

1年間に新しく病気になった患者さんの推定数
(2次医療圏別に推計、総計で361人)

調査から計算された実際の新規患者さん数
(1年間に、中核医療機関を新規受診した患者さん総数247人)

2. 治療を受けられる大きな病院はどこにありますか?

診療所数
127.3



全国平均より、恵まれています。

結論から申しますと、徳島県の医療体制は非常に恵まれています。

下の5角形（レーダーチャートと言います）をご覧ください。

人口あたりで比較してみると、医者・看護師など医療従事者の数、病院や診療所の数が、全国トップレベルなのです。ご存じでしたか?

いやいや人口密度が低いから国籍あたりに直せばそんなに多くないぞ、過疎化・高齢化も進んでいるぞ、大都市圏に比べて恵まれていないはずだ、という声もあることでしょう。たしかに、受療率（医療機関で受診する患者数）やがん患者さんの数は、全国平均より高くなっています。

実際のところどうなのだろうかということで、高度な治療を要する白血病・悪性リンパ腫・多発性骨髄腫の患者さんを対象に、どの程度県内で専門医の治療を受けているか調査してみました。それを示したのが、右の地図です。

ほぼ県内で治療を受けられています。

調べてみた結果、白血病・悪性リンパ腫、多発性骨髄腫の患者さんの場合、ほとんどが県内の専門医による治療を受けていることが分かりました。ちゃんと高度医療が提供されているわけですね。

これは最初に患者さんを診る地域の開業医が、きちんと専門医や病院へ紹介しているためと考えられます。

もちろん課題も見つかりました。専門医がいたり専門診療科があったりする大きな病院が徳島市など県の東北部に集中しており、それ以外の地域の患者さんは遠距離通院する必要があるようです。また、逆に東北部の基幹病院から僻地の病院に非常勤で頻繁されている医師にとっても、この移動は大きな負担になっているようです。

今後さらに医療サービスの向上を図るには、県の東北部以外の患者さんに対して、何らかの手助けが必要であると考えられます。医療者だけの力では困難が難しい面もありますので、県民の皆様にもご協力いただければ幸いです。

が人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に関する研究
(厚生労働科学研究費補助金事業)
研究班：東京大学医科学研究所 癌医療ヒューマンネットワークシステム部門
東京都港区白金台4-6-1 03-5449-2000

ご意見ください

抽選で100名様に差し上げます。『東大のがん治療医が癌になって』(ロハスメディア、1575円)

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