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表 1 日本の添付文書におけるトランスポーター記載状況の推移

Drugs	Transporter	Approval	2000/ 1	2001/ 4	2002/10	2003/ 4	2004/ 4	2005/ 1	2006/ 7
adefovir pivoxil	human organic anion transporter 1 (OATP1)	2004	—	—	—	—	—	v	v
atorvastatin calcium hydrate	P-glycoprotein	2000	—	v	v	v	v	v	v
clarithromycin	P-glycoprotein	1991						v	v
clarithromycin/ lansoprazole/ amoxicillin	P-glycoprotein	2002	—	—	—			v	v
digitoxin	P-glycoprotein	1952				v	v	v	v
digoxin	P-glycoprotein	1956		v	v	v	v	v	v
fexofenadine hydrochloride	P-glycoprotein	2001	—	v	v	v	v	v	v
ivermectin	P-glycoprotein	2002	—	—	—	v	v	v	v
lanatoside C	P-glycoprotein	1976				v	v	v	v
metildigoxin	P-glycoprotein	1999		v	v	v	v	v	v
probenecid	organic anion transporter	1956				v	v	v	v
rosuvastatin calcium	OATP-C (OATP-2)	2005	—	—	—	—	—	—	v
	P-glycoprotein	2005	—	—	—	—	—	—	v
saquinavir mesylate	P-glycoprotein	1997					v	v	v
valaciclovir hydrochloride	peptide transporter (PEPT1)	2000	—	v	v	v	v	v	v
valganciclovir hydrochloride	peptide transporter (PEPT1)	2004	—	—	—	—	—	—	v

—： 未承認

v ： 記載あり

図1　日本の添付文書におけるトランスポーター記載数の推移

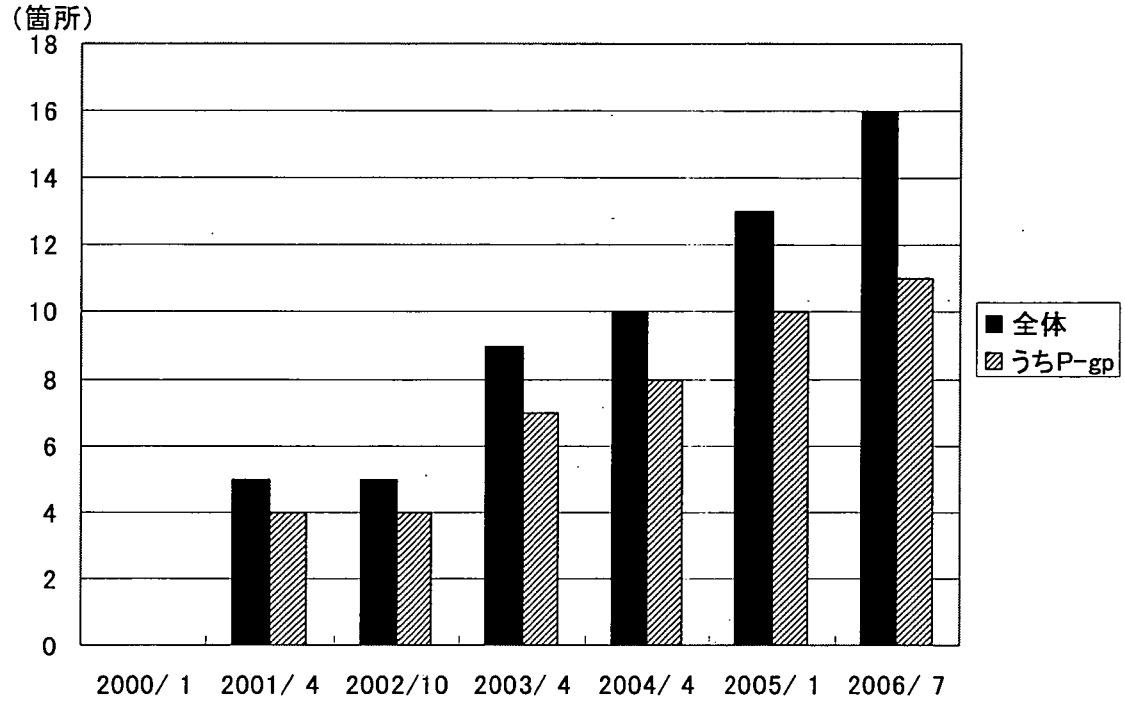

表 2 日本の添付文書におけるトランスポーター記載

Drugs	Status	Transporter	Remark
adefovir pivoxil	interaction	human organic anion transporter 1 (OATP1)	
atorvastatin calcium	interaction	P-glycoprotein	
clarithromycin	interaction	P-glycoprotein	
clarithromycin/lansoprazole /amoxicillin	interaction	P-glycoprotein	
digitoxin	interaction	P-glycoprotein	
digoxin	interaction	P-glycoprotein	
fexofenadine hydrochloride	interaction, pharmacokinetics	P-glycoprotein	
ivermectin	pharmacokinetics	P-glycoprotein	
lanatoside C	interaction	P-glycoprotein	
metildigoxin	interaction	P-glycoprotein	
probenecid	interaction	organic anion transporter	
rosuvastatin calcium	pharmacokinetics	OATP-C(OATP-2)	
		P-glycoprotein	denial
saquinavir mesylate	interaction	P-glycoprotein	
valaciclovir hydrochloride	pharmacokinetics	peptide transporter (PEPT1)	
valganciclovir hydrochloride	pharmacokinetics	peptide transporter (PEPT1)	

表 3 米国の添付文書におけるトランスポーター記載

Drugs	Status	Transporter	Remark
aprepitant	Precautions	P-glycoprotein	denial
caspofungin acetate	Precautions	P-glycoprotein	denial
eplerenone	Precautions	P-glycoprotein	denial
ertapenem	Precautions/Clinical pharmacology	P-glycoprotein	denial
ethinyl estradiol/desogestrel	Precautions	P-glycoprotein	
ethinyl estradiol/drospirenone	Precautions	P-glycoprotein	
ethinyl estradiol/etonogestrel	Precautions	P-glycoprotein	
ethinyl estradiol/levonorgestrel	Precautions	P-glycoprotein	
ethinyl estradiol/norelgestromin	Precautions	P-glycoprotein	
ethinyl estradiol/norgestimate	Precautions	P-glycoprotein	
ethinyl estradiol/norgestrel	Precautions	P-glycoprotein	
fexofenadine HCl/pseudoephedrine HCl	Precautions	P-glycoprotein	
micafungin sodium	Precautions/Clinical pharmacology	P-glycoprotein	denial
pramipexole dihydrochloride	Precautions	anionic transporter	denial
pravastatin sodium	Precautions	P-glycoprotein	
pregabalin	Clinical pharmacology	system L transporter	
propranolol hydrochloride	Clinical pharmacology	P-glycoprotein	denial
ramelteon	Precautions	P-glycoprotein	denial
ribavirin	Clinical pharmacology	es-type equilibrative nucleoside	
ribavirin/interferon alfa-2b	Clinical pharmacology	es-type equilibrative nucleoside	
saquinavir mesylate	Precautions	P-glycoprotein	
sirolimus	Warnings/Precautions/Clinical pharmacology	P-glycoprotein	
tacrolimus	Precautions	P-glycoprotein	
tipranavir	Precautions/Clinical pharmacology	P-glycoprotein	
voriconazole	Precautions	P-glycoprotein	denial

表 4 英国の添付文書におけるトランスポーター記載

Drugs	Status	Transporter	Remark
adefovir dipivoxil	Special warnings	human Organic Anion Transporter 1 (hOAT1)	
aprepitant	Interaction	P-glycoprotein	denial
atorvastatin calcium	Interaction/Pharmacokinetic properties	P-glycoprotein	
bosentan monohydrate	Interaction/Pharmacokinetic properties	P-glycoprotein	
caspofungin acetate	Interaction/Pharmacokinetic properties	P-glycoprotein	denial
clarithromycin	Interaction	P-glycoprotein	
desloratadine	Pharmacokinetic properties	P-glycoprotein	denial
dispersible	Pharmacokinetic properties	MRP2	
		MXR (BCRP)	
doxorubicin citrate	Interaction/Pharmacokinetic properties	P-glycoprotein	
dutasteride	Interaction	P-glycoprotein	denial
eplerenone	Interaction	P-glycoprotein	denial
erlotinib hydrochloride	Interaction	P-glycoprotein	
ertapenem sodium	Interaction/Pharmacokinetic properties	P-glycoprotein	denial
loperamide hydrochloride	Interaction	P-glycoprotein	
posaconazole	Interaction	P-glycoprotein	
pravastatin sodium	Pharmacokinetic properties	P-glycoprotein	denial
		other transport proteins	
ribavirin	Pharmacokinetic properties	es-type equilibrative nucleoside transporter	
rimonabant	Interaction	P-glycoprotein	denial
ritonavir	Interaction	P-glycoprotein	
rosuvastatin calcium	Pharmacokinetic properties	OATP-C	
saquinavir mesylate	Interaction/Pharmacokinetic properties	P-glycoprotein	
sirolimus	Interaction/Pharmacokinetic properties	P-glycoprotein	
sorafenib tosylate	Interaction	P-glycoprotein	
tadalafil	Interaction	P-glycoprotein	
tenofovir disoproxil	Special warnings/Interaction	human organic anion transporter 1 (hOAT1)	
tipranavir	Interaction/Pharmacokinetic properties	P-glycoprotein	
voriconazole	Interaction	P-glycoprotein	denial

図 2　各国の添付文書でのトランスポーター記載状況

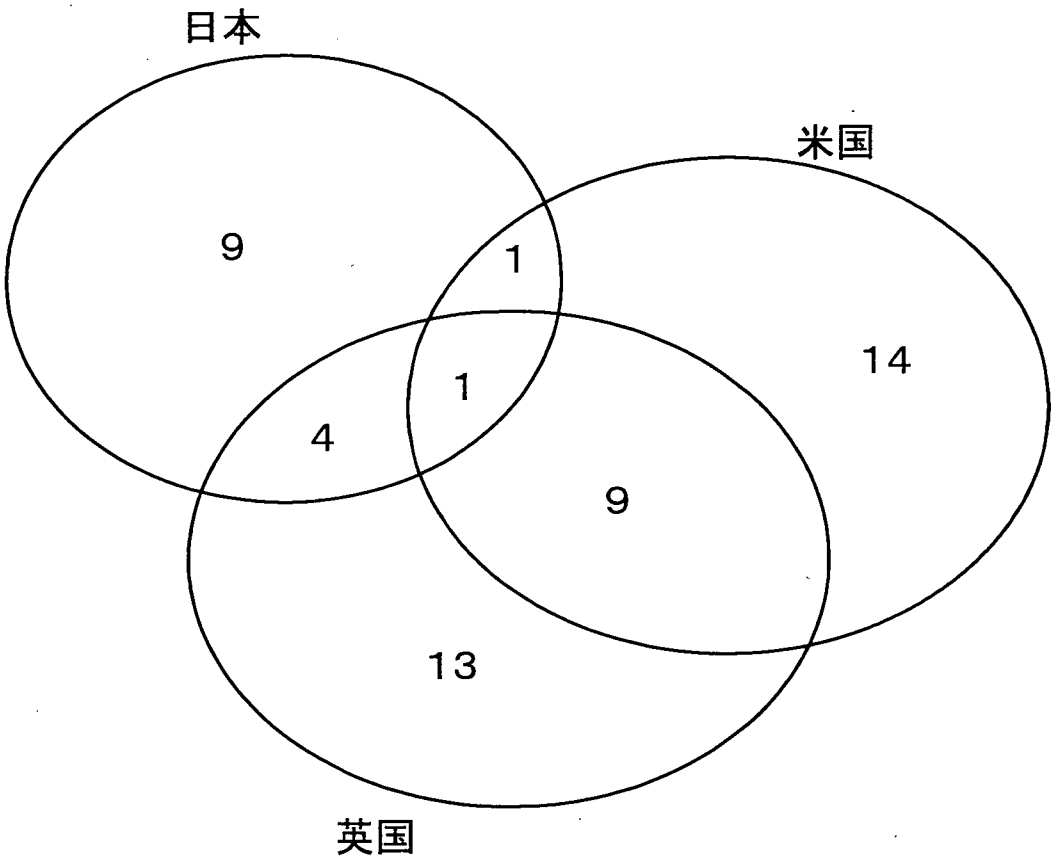

表 5 添付文書に記載されているトランスポーターに関する研究報告

記載国			Drugs	Transporter			PK study (change in AUC)
JP	US	UK		substrate	inhibitor	inducer	
v		v	adefovir	MRP4, MRP5, OAT1, OCT3	OAT1	—	—
	v	v	aprepitant	—	—	—	—
v		v	atorvastatin	OATP1B1	P-gp, MRP2, OATP1B1	—	cyclosporin (7.4 fold), erythromycin (1.3 fold), 1.2 fold for digoxin AUC
		v	bosentan	—	—	—	cyclosporin (2 fold)
	v	v	caspofungin	OATP1B1, OATP1B3	P-gp, NTCP, OAT1, OATP1B1, OCT1	—	—
v		v	clarithromycin	P-gp	Pg-p, OAT2	—	decrease renal clearance of digoxin (-48%)
		v	desloratadine	—	P-gp	—	—
v			digitoxin	P-gp	OATP4C1	—	—
v			digoxin	P-gp, OATP1B3, OATP1C1, OATP4C1, OST	P-gp, OATP4C1	P-gp	verapamil (1.8 fold), quinidine (2.5 fold), nifedipine (1.2 fold), diltiazem (1.6 fold), erythromycin (2 fold)
		v	dispersible	—	—	—	—
		v	doxorubicin	BCRP, BSEP, P-gp, MRP1, MRP6	BCRP, P-gp, MRP1, MRP3, MRP7	—	verapami (2 fold), cyclosporin (1.8 fold)
		v	dutasteride	—	—	—	—
	v	v	eplerenone	—	—	—	—
		v	erlotinib	—	—	—	—
	v	v	ertapenem	—	—	—	—
	v		ethinyl estradiol	MRP2, MRP3(as 3O-glucronide)	—	—	—
v	v		fexofenadine	P-gp, OATP1A2, OATP2B1	P-gp	—	azithromycin (1.67 fold), ketoconazole (2.6 fold), erythromycin (2.1 fold), probenecid (1.5 fold)
v			ivermectin	P-gp	P-gp	—	—
v			lanatoside C	—	—	—	—
		v	loperamide	P-gp	P-gp	—	ritonavir (2.7 fold), quinidine (2.5 fold)
v			metildigoxin	—	—	—	—
	v		micafungin	—	—	—	—
		v	posaconazole	—	—	—	—
	v		pramipexole	—	—	—	—
	v	v	pravastatin	BCRP, P-gp, MRP2, OATP1A2, OATP1B1, OATP2B1	BCRP, P-gp, MRP2, OAT1, OAT2, OAT3, OAT4, OATP1B1	—	propranolol (0.8 fold), cyclosporin (7.9 fold), ritonavir/saquinavir (0.5 fold), gemfibrozil (1.8 fold), rifampicin (0.7 fold), itraconazole (1.5 fold)
	v		pregabalin	—	—	—	—
v			probenecid	—	P-gp, MRP1 MRP2, MRP3, MRP4, MRP5, MRP6, MRP8, OAT1, OAT2, OAT3, OAT4, OCTN2	—	1.3 fold for valaciclovir, 1.5 fold for aciclovir, 2 fold for cinoxacin, 2.4 fold for cepharadine, 2.1 fold for cefmenoxine, 2.4 fold for cefoxin, 1.5 fold for ganciclovir, 3.6 fold for clofibrate
	v		propranolol	P-gp, OCT2	P-gp, NTCP, OCT2	—	0.77 fold for pravastatin
	v		ramelteon	—	—	—	—
	v	v	ribavirin	—	—	—	—
		v	rimonabant	—	—	—	—
		v	ritonavir	Pgp, MRP2	BCRP, P-gp, MRP1, OATP1A2, OATP1B1	P-gp, MRP1, MRP2	58 fold for saquinavir, 2.7 fold for loperamide, 0.5 fold for pravastatin
v		v	rosuvastatin	—	—	—	gemfibrozil (1.9 fold), cyclosporin (7.1 fold)
v	v	v	saquinavir	P-gp, MRP1, MRP2	BCRP, P-gp, OATP1A2, OATP1B1	P-gp	ritonavir (58 fold), rifampicin (0.3 fold), ketoconazole (2.9 fold), erythromycin (2 fold)
	v	v	sirolimus	P-gp	P-gp	—	cyclosporin (1.5 fold)
		v	sorafenib	—	—	—	—
	v		tacrolimus	P-gp	P-gp	P-gp	diltiazem (4.3 fold), ketoconazole (2 fold)
		v	tadalafil	—	—	—	—
		v	tenofovir	—	—	—	—
	v	v	tipranavir	—	—	—	—
v			valaciclovir	—	—	—	probenecid (1.3 fold)
v			valganciclovir	—	—	—	—
	v	v	voriconazole	—	—	—	—

表 6 トランスポーターを介した有害事象報告、メカニズム研究と添付文書記載状況

影響を受ける薬剤	影響を与える薬剤	有害事象	症例報告での推定機序	メカニズム研究	添付文書		
					JP	US	UK
atorvastatin	esomeprazole [1]	横紋筋融解症、房室ブロック	P-gp阻害	atorvastatin: OATP1B1阻害[2] omeprazole: P-gp阻害[3]、BCRP阻害[4]	記載なし	記載なし	記載なし
colchicine	cyclosporin [5]	多臓器不全	P-gp阻害	colchicine: P-gp基質[6][7]、P-gp阻害[6][8]、MRP1基質[9] cyclosporin: P-gp阻害[10]、MRP1阻害[11]、MRP2阻害[12][13]、OATP1B1阻害[14]	併用注意 機序は不明	未承認	Drug interaction 筋障害
cyclophosphamide	roxithromycin [15]	毒性増強	CYP3A4, P-gp阻害	cyclophosphamide: P-gp阻害[16]	記載なし	入手できず	記載なし
digoxin	clarithromycin [17]	digoxin濃度上昇、digitalis中毒(3/26)	記載なし	digoxin: P-gp基質[18]、OATP1B3基質[19]、OATP4C1基質[20]、OST基質[21]	併用注意 腸内細菌叢による代謝またはP-gp阻害	Drug interaction 腸内細菌による不活化阻害のため一部の人で血中濃度2倍まで増加	Drug interaction macrolide antibiotics
	[25]	腎移植必要な患者。digoxin濃度上昇、digitalis中毒(2/6)	小腸または毛細胆管のP-gp抑制	clarithromycin: P-gp阻害[22][23]、OAT2阻害[24]			
digoxin	sertraline, paroxetine, fluoxetine, fluvoxamine [26]	併用投与によるdigoxin毒性のリスク上昇(抗うつ剤間の有意差なし)	SSRIのP-gp抑制作用は臨床上有意でない	digoxin: P-gp基質[18]、OATP1B3基質[19]、OATP4C1基質[20]、OST基質[21] sertraline, paroxetine, fluoxetine, fluvoxamine: P-gp阻害[27]	記載なし	記載なし	記載なし
levothyroxine	raloxifene [28]	同時投与で増量必要。分割投与で甲状腺機能亢進	吸収阻害(機序不明)	levothyroxine: P-gp誘導(十二指腸、in vivo)[29]	記載なし	記載なし	入手できず
pilsicainide	cetirizine [30]	血中濃度増加、副作用増強、腎クリアランス低下	P-gp, OATP2競合阻害	なし	記載なし	未承認	未承認
pravastatin	colchicine [31]	筋障害(下肢脱力)、両薬剤中止により回復	P-gp阻害	pravastatin: P-gp, BCRP, MRP2, OATP1A2,OATP1B1,OATP2B1基質[32][33][34] colchicine: P-gp基質[6][7]、P-gp阻害[6][8]、MRP1基質[9]	記載なし	記載なし	記載なし
tacrolimus	metronidazole [35]	tacrolimus血中濃度増加、血清クレアチニン値上昇	CYP3A4, P-gp阻害	tacrolims: P-gp基質[36][37]	記載なし	記載なし	記載なし
vinblastine	ritonavir, lopinavirを含む抗HIV療法 [38]	毒性増強	CYP, P-gp阻害	vinblastine: P-gp基質[39]、P-gp阻害[40]、MRP2基質[12] ritonavir: P-gp阻害[41][42]、MRP1阻害[43]、OATP1A2阻害[44]、OATP1B1阻害[42] lopinavir: P-gp阻害[45]	記載なし	入手できず	記載なし
vincristine	itraconazole, ketoconazole, cyclosporine, isoniazid, nifedipine [46]	vincristine毒性の増強	CYP3A, P-gp阻害	vincristine: P-gp基質[6][47]、MRP1基質[48]、MRP2基質[13] itraconazole:P-gp阻害[49] ketocoxazole: P-gp阻害[10]、OATP1A2阻害[44] cyclosporin: P-gp阻害[10]、MRP1阻害[11]、MRP2阻害[12][13]、OATP1B1阻害[14] nifedipine: P-gp阻害[50]	併用注意 アゾール系抗真菌薬(ketoconazole):CYP3A4阻害	入手できず	Drug interaction CYP3A阻害剤、itraconazoleでは神経・筋毒性の増強
verapamil	erythromycin [51]	房室ブロック、QTc延長	CYP3A4, P-gp阻害	verapamil: P-gp基質[6][52] erythromycin: P-gp阻害[6][10]、MRP1阻害[53]、OATP1A2阻害[44]、OAT2阻害[24]	記載なし	Drug interaction CYP3A4阻害による血中濃度上昇	記載なし
warfarin	mercaptopurine [54]	warfarinの増量が必要	消化管吸収阻害、肝代謝酵素誘導	mercaptopurine: MRP4基質[55]、MRP5基質[56]	併用注意 作用の増強、減弱	PT/INR減少	入手できず

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分担研究報告書

抗がん剤併用療法における有害事象発生例の調査・分析に関する研究

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研究要旨：トラスツズマブは時に重篤な心障害、Infusion reaction（ＩＲ）を起こす。この副作用に対する予測やモニタリングは薬物治療を行う上で重要である。国立がんセンター中央病院における診療録調査を通じ、前治療歴の有無や抗がん剤併用時における関連性を明らかにし、これらの予測可能性を検討した。

Ａ．研究目的

乳がんでは多剤併用療法の有用性が確立され、標準治療レジメンとして、不可逆的な心毒性を有するアンスラサイクリン含有レジメン及びタキサン系レジメンが中心的な役割を担っている。また悪性度が高く予後不良とされる乳がん細胞の膜蛋白である HERⅡ蛋白陽性患者においては、上記レジメンに加えたトラスツズマブの投与が標準治療とされている。今回トラスツズマブの心障害、ＩＲの発生状況に関する調査を行い、抗がん剤治療歴や抗がん剤併用時等のリスクファクターを有する場合での心毒性、ＩＲの発生状況を明らかにし、より安全な薬物治療に資することを目的とする。

Ｂ．研究方法

国立がんセンター中央病院におけるトラスツズマブ投与歴を有する乳がん患者に対し、診療録及びオーダリングシステムを用い調査した。対象は、本薬剤が承認された 2001 年 6 月から 2006 年 12 月の間に本薬剤の投与歴を有する者とし、321 名であった。調査項目は、患者背景（年齢、身長、体重、既往歴、ＨＥＲ２発現及びホルモン受容体発現等）、アンスラサイクリン系抗がん剤（Anth 系）及び胸部放射線前治療歴、抗がん剤投与状況（単独・併用：図 1）に関連した心障害、ＩＲの発現状況とした。

Ｃ．研究結果

患者背景として年齢・身長・体重中央値は、54 歳（26-86）・154.9cm（137.1-180.5）・52.7kg（31-87.5）であった（表１）。対象患者 321 名のうち心障害発現症例は 17 名（5.3%）であった。メーカー使用成績調査（1142 例のうち 28 例）と比較すると、ＲＲ＝2.16（1.20-3.89）となり、本調査結果は既存の情報よりも多く検出された。またＩＲは 97 例（30.2%）であり、メーカー使用成績調査（1142 例のうち 367 例）との比較では 0.94（0.78-1.13）となり、発生割合に違いは見られなかった（表２）。Anth 系抗がん剤及び胸部放射線前治療歴の有無と心障害発現との間には、いずれも違いは見られなかった（表３、ＲＲ＝1.34（0.48-3.71）、ＲＲ＝0.59（0.21-1.68））。Anth 系抗がん剤前治療歴の有無とＩＲ発現について

は、前治療歴無し群は有り群と比べ発生割合は高かった（表４、ＲＲ＝0.70（0.50-0.97））。トラスツズマブ単独群とパクリタキセル、ドセタキセル、ビノレルビン併用群では、心障害、ＩＲともに発生割合に違いは見られなかったが、パクリタキセル併用群ではＩＲの発生割合が低い傾向が示唆され（表６）、これはPre Med 投与群との比較においても同様であった（表７）。

D．結論及び考察

トラスツズマブ投与における心障害は、メーカー報告とは差があったものの前治療歴や併用薬剤の差異には違いがなかった。トラスツズマブ投与の安全性が高いと思われる反面、心障害例数が少なく更なる検討が必要と思われる。今後は、承認拡大による術前・術後療法におけるトラスツズマブの使用頻度が増すことが予測されており、心障害のモニタリングは重要である。

ＩＲの発現率は約 30%であり、患者への十分な説明が必要と思われる。トラスツズマブ投与時のＩＲにおいてAnth 系抗がん剤の前治療歴無し群は、有り群と比べ発生割合は多かった。この知見に関する報告はなく、今後確認を重ねていく必要がある。さらにステロイド剤前投薬がＩＲ発生割合を軽減すると思われ、IR 発現の予測が可能であれば、ＩＲリスクの高い患者にはＩＲ予防法としてステロイド剤の前投薬の選択も一案と考えられた。

E．健康危険情報

該当なし

F．研究発表

1．論文発表

なし

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）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

図１　抗がん剤投与方法の詳細

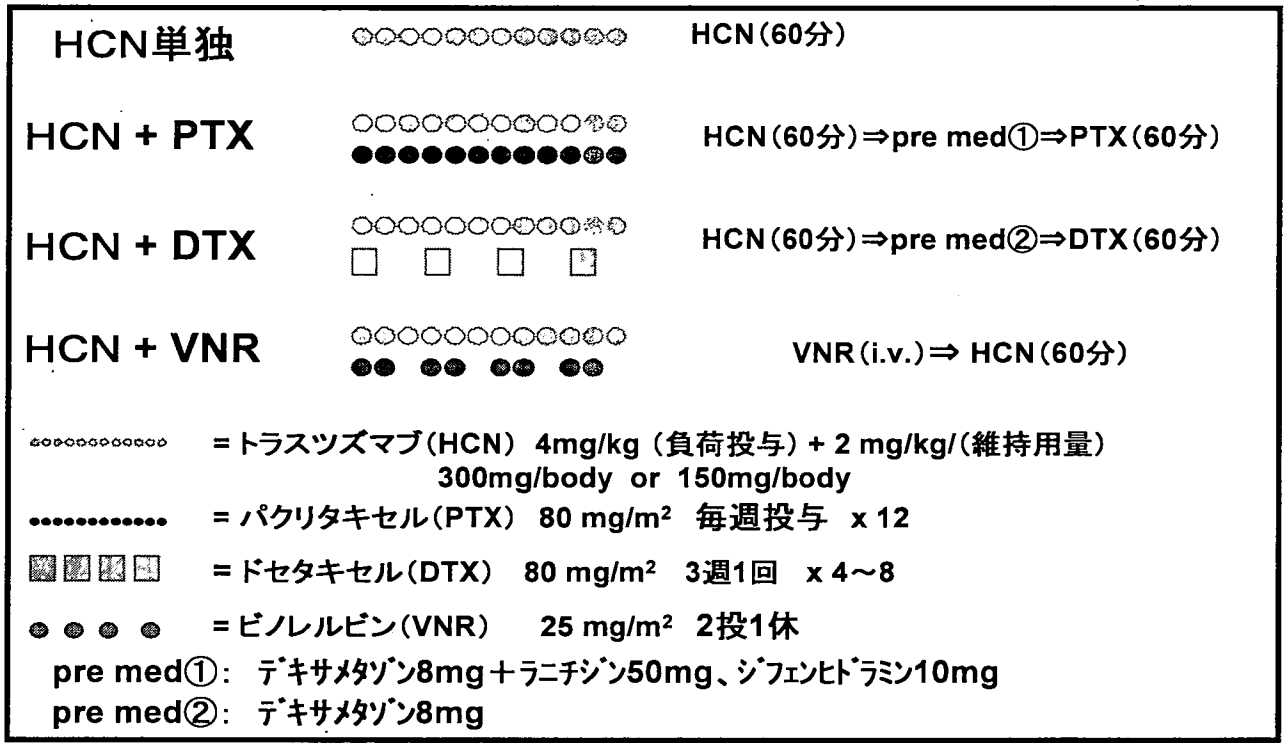

表１　患者背景

患者背景			評価可能人数
年齢(中央値)		54 (26-86)	321
性別(M/F)		2/319	321
身長cm		154.9 (137.1-180.5)	320
体重kg		52.7 (31-87.5)	311
喫煙歴有り		46	295
飲酒歴有り		85	295
ｱﾚﾙｷﾞｰ歴(食事)		18	314
ｱﾚﾙｷﾞｰ歴(薬剤)		42	315
HER2(3+)		258	309
HER2(2+ FISH+)		51	309
HR(ER/PgR and/or +)		123	270
HR(ER/PgR -/-)		147	270
閉経		225	295
既往歴	心疾患	11	321
	肺疾患	16	321
	高血圧	36	321
	糖尿病	10	321

表２　心障害と Infusion Reaction の発現数

	イベント	あり	なし	全人数	Relative Risk (95%CI)
診療録調査	心毒性	16 (5.2%)	291	321	2.16
	Infusion Reaction	98 (31.4%)	214	321	(1.20-3.89)
メーカー使用成績調査	心毒性	28 (2.5%)	1114	1142	0.94
	Infusion Reaction	367 (32.1%)	928	1142	(0.78-1.13)

表３　前治療歴の有無と心障害

前治療歴	Anthra系抗がん剤有り	Anthra系抗がん剤無し	全患者数	Relative Risk (95%CI)
心毒性有り	12	5	17	1.34
心毒性無し	194	110	304	(0.48-3.71)
前治療歴	胸部放射線治療有り	胸部放射線治療無し	全患者数	Relative Risk (95%CI)
心毒性有り	3	14	17	0.59
心毒性無し	83	221	304	(0.21-1.68)

表４　前治療歴の有無と IR

前治療歴	Anthra系抗がん剤有り	Anthra系抗がん剤無し	全患者数	Relative Risk (95%CI)
IR有り	54	43	97	0.70
IR無し	152	72	224	(0.50-0.97)
前治療歴	胸部放射線治療有り	胸部放射線治療無し	全患者数	Relative Risk (95%CI)
IR有り	28	69	97	1.28
IR無し	54	170	224	(0.93-1.75)

表５　併用薬剤と心障害、IR の発現率

併用薬剤	心障害有り		心障害無し		対象患者数	IR有り		IR無し		対象患者数
	延べ人数	%	延べ人数	%		人数	%	人数	%	
HCN単独	2	4.4	43	95.6	45	49	34	96	66	145
PTX併用	11	4.5	231	95.5	242	37	25	112	75	149
DTX併用	4	5.8	65	94.2	69	5	39	8	62	13
VNR併用	3	2.6	112	97.4	115	5	46	6	55	11

注）心障害有り無し：HCN 単独群　：　HCN しか投与歴が無い群

PTX 併用、DTX 併用、VNR 併用群　：　一度でも左記レジメンの投与歴が有る群（延べ人数）

IR 有り無し　：IR 有り：IR を起こした際のレジメンをカウント

IR 無し：初回レジメンをカウント

表６　併用薬剤と心障害、IR の差異

	PTX併用	HCN併用	Relative Risk (95%CI)		PTX併用	HCN併用	Relative Risk (95%CI)
心障害有り	11	2	1.02	IR有り	37	49	0.73
心障害無し	231	43	(0.25-4.23)	IR無し	112	96	(0.51-1.05)
	DTX併用	HCN併用	Relative Risk (95%CI)		DTX併用	HCN併用	Relative Risk (95%CI)
心障害有り	4	2	1.30	IR有り	5	49	1.14
心障害無し	65	43	(0.25-6.81)	IR無し	8	96	(0.55-2.35)
	VNR併用	HCN併用	Relative Risk (95%CI)		VNR併用	HCN併用	Relative Risk (95%CI)
心障害有り	11	2	0.59	IR有り	5	49	0.59
心障害無し	231	43	(0.10-3.42)	IR無し	6	96	(0.30-1.17)

表７　Pre Med と IR の差異

	Pre Med有り (PTX+DTX)	HCN併用	Relative Risk (95%CI)		Pre Med有り (PTX+DTX)	Pre Med無し (VNR+HCN)	Relative Risk (95%CI)
IR有り	42	49	0.77	IR有り	42	54	0.75
IR無し	120	96	(0.54-1.09)	IR無し	120	102	(0.54-1.05)