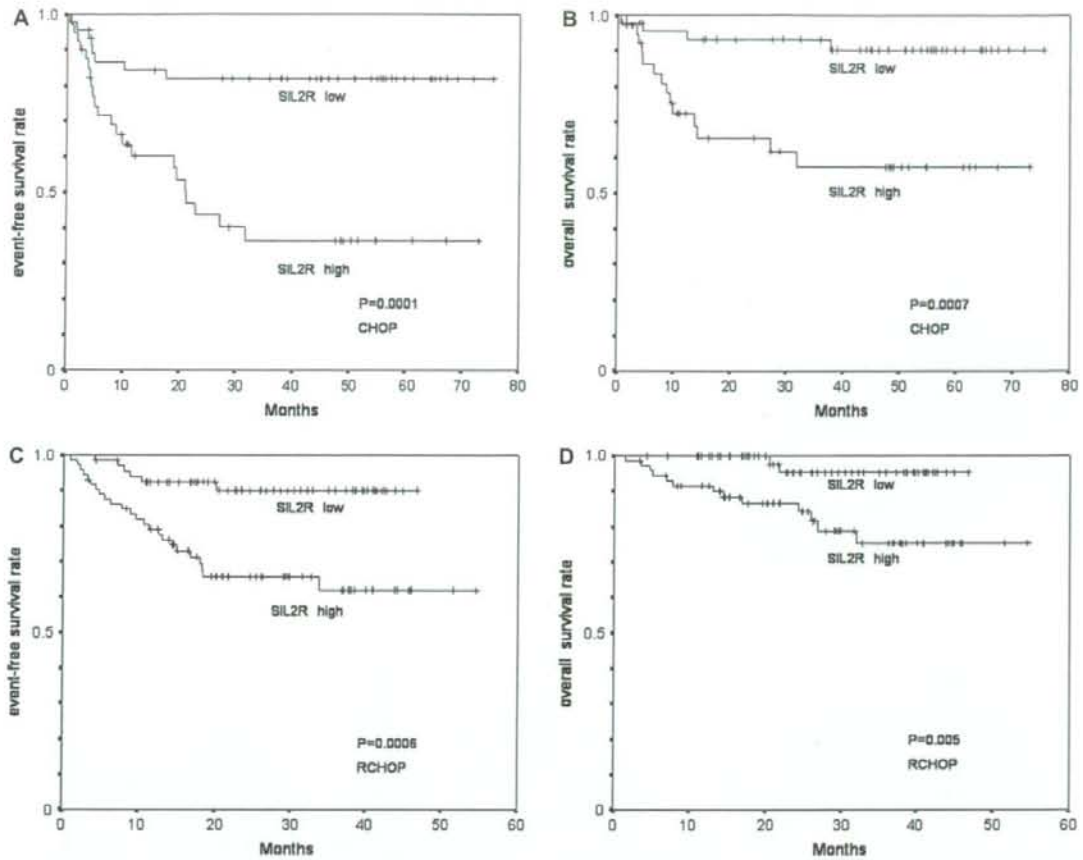

Figure 1. Event-free survival (EFS) and overall survival (OS) curves for diffuse large B-cell lymphoma patients treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and rituximab-combined CHOP (RCHOP) in relation to soluble interleukin-2 receptor (SIL-2R). EFS (A) and OS (B) curves according to low ($n = 47$) versus high ($n = 40$) SIL-2R in the CHOP group. EFS (C) and OS (D) curves according to low ($n = 67$) versus high ($n = 74$) SIL-2R in the RCHOP group.

Table 2. Analysis of 2-year survival rate according to CHOP and RCHOP therapy in both SIL-2R groups

Clinical outcome	Low SIL-2R			High SIL-2R		
	CHOP	RCHOP	*P*	CHOP	RCHOP	*P*
2-year survival						
EFS (%)	82	90	0.160	43	66	0.0010
OS (%)	93	95	0.310	65	84	0.0020

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; RCHOP, rituximab-combined CHOP; SIL2R, soluble interleukin-2 receptor; EFS, event-free survival; OS, overall survival.

results were obtained in patients receiving chemotherapy, and the prognostic value of SIL-2R has not been assessed in rituximab-combined treatment.

In the present study, univariate analysis showed that SIL-2R retained its prognostic value in DLBCL patients treated with RCHOP, as well as in those receiving CHOP alone. Multivariate analysis also showed that SIL-2R was an independent significant prognostic factor after adjustment for IPI risk factors and independently associated with significantly decreased EFS and moderately decreased OS after adjustment by two-categorized IPI in both the CHOP and RCHOP groups. On the other hand, the clinical outcome of patients with high SIL-2R was significantly improved by addition of rituximab to the chemotherapy, in contrast to the lack of any difference in the patients with low SIL-2R. To our knowledge, this is the first report to demonstrate the prognostic value of SIL-2R in DLBCL patients treated with rituximab-combined chemotherapy.

Although the present study was not a randomized prospective one, and possibly biased by factors other than IPI and SIL-2R, the distribution of baseline characteristics, including IPI factors, was similar between the two treatment groups. On the other hand, the population employed in the present analysis had more limited disease and a favorable IPI score compared with those in previous studies of DLBCL [13–17]. This might account for the better outcome of our

Table 3. The effects of clinical factors on EFS and OS in CHOP by univariate analysis using Cox proportional hazard model

	Variable	HR	95% CI	P value
CHOP				
EFS	SIL-2R			
	Low	1.00		
	High	4.30	1.94–9.74	<0.001
	Age			
	≤60	1.00		
	>60	1.48	0.64–3.46	0.36
	LDH			
	Normal	1.00		
	High	2.65	0.80–8.74	0.11
	PS			
	0–1	1.00		
	2–3	4.10	1.64–10.25	0.003
	Stage			
	I, II	1.00		
	III, IV	3.75	1.79–7.83	<0.001
	Extranodal sites			
	0–1	1.00		
	≤2	3.24	1.54–6.81	0.002
	IPI			
	L/L-I	1.00		
	H/H-I	3.97	1.91–8.25	<0.001
OS	SIL-2R			
	Low	1.00		
	High	5.64	1.84–17.23	0.002
	Age			
	≤60	1.00		
	>60	2.20	0.64–7.61	0.21
	LDH			
	Normal	1.00		
	High	4.71	0.63–35.41	0.13
	PS			
	0–1	1.00		
	2–3	7.18	2.44–21.13	<0.001
	Stage			
	I, II	1.00		
	III, IV	5.15	1.92–13.81	0.001
	Extranodal sites			
	0-1	1.00		
	≤2	4.24	1.64–10.98	0.003
	IPI			
	L/L-I	1.00		
	H/H-I	7.28	2.69–19.67	<0.001
RCHOP				
EFS	SIL-2R			
	Low	1.00		
	High	4.20	1.72–10.33	0.002
	Age			
	≤60	1.00		
	>60	1.38	0.61–3.11	0.44
	LDH			
	Normal	1.00		
	High	1.41	0.68–2.93	0.35
	PS			
	0–1	1.00		
	2–3	3.62	1.35–8.46	0.003
	Stage			
	I, II	1.00		
	III, IV	3.42	1.64–7.11	0.001
	Extranodal sites			
	0–1	1.00		
	≤2	3.43	1.67–7.03	<0.001
	IPI			
	L/L-I	1.00		
	H/H-I	3.40	1.82–6.25	<0.001
OS	SIL-2R			
	Low	1.00		
	High	6.42	1.45–28.45	0.01
	Age			
	≤60	1.00		
	>60	3.50	0.79–15.52	0.10
	LDH			
	Normal	1.00		
	High	1.69	0.58–4.97	0.34
	PS			
	0–1	1.00		
	2–3	5.97	2.03–17.54	0.001
	Stage			
	I, II	1.00		
	III, IV	2.46	0.89–6.79	0.08
	Extranodal sites			
	0–1	1.00		
	≤2	2.65	0.96–7.33	0.06
	IPI			
	L/L-I	1.00		
	H/H-I	4.03	1.43–11.34	0.08

EFS, event-free survival; OS, overall survival; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; RCHOP, rituximab-combined CHOP; HR, hazard ratio; CI, confidential interval; SIL2R, soluble interleukin-2 receptor; LDH, lactate dehydrogenase; PS, performance status; IPI, International Prognostic Index; L/L-I, low or low-intermediate; H/H-I, high or high-intermediate.

patients than for those in previous reports such as that by Coiffier et al. [14] who observed 2-year survival rates of 70% and 57% in elderly patients treated with RCHOP and CHOP, respectively. Even with the excellent outcome we observed, however, the prognostic value of SIL-2R was significant and greater than that of other IPI risk factors. To allow our present results to be generalized to routine patient care, these findings should be validated in a variety of patient populations.

A number of prognostic markers have been identified in patients with DLBCL treated by chemotherapy alone [19–21], some of which have been reassessed and shown not to be associated with prognosis in patients receiving rituximab-combined chemotherapy [22–24]. BCL2 overexpression was reported to be associated with poorer survival in patients treated with CHOP-like regimens [19], but its prognostic value was not confirmed in patients receiving rituximab-combined chemotherapy in several studies, indicating that addition of rituximab overcomes the negative influence of BCL2

Table 4. Multivariate Cox proportional hazard regression analysis for SIL-2R and IPI risk factors in both treatment groups

	Variable	HR	95% CI	*P* value
CHOP				
EFS	SIL-2R			
	Low	1.00		
	High	2.74	1.05–7.14	0.04
	PS			
	0–1	1.00		
	2–3	2.12	0.73–6.14	0.17
	Stage			
	I, II	1.00		
	III, IV	1.82	0.65–5.09	0.25
	Extranodal sites			
	0–1	1.00		
	≤2	1.09	0.38–3.10	0.87
OS	SIL-2R			
	Low	1.00		
	High	3.53	1.03–12.95	0.05
	LDH			
	Normal	1.00		
	High	3.21	0.40–25.51	0.27
	PS			
	0–1	1.00		
	2–3	3.60	0.98–13.20	0.05
	Stage			
	I, II	1.00		
	III, IV	2.00	0.51–7.87	0.32
	Extranodal sites			
	0–1	1.00		
	≤2	0.86	0.22-0.83	0.83
RCHOP				
EFS	SIL-2R			
	Low	1.00		
	High	2.65	1.01–7.30	0.05
	PS			
	0–1	1.00		
	2–3	1.66	0.62–4.42	0.31
	Stage			
	I, II	1.00		
	III, IV	1.69	0.65–4.42	0.28
	Extranodal sites			
	0–1	1.00		
	≤2	1.36	0.50–3.67	0.55
OS	SIL-2R			
	Low	1.00		
	High	5.09	1.00–25.88	0.05
	Age			
	≤60	1.00		
	>60	2.45	0.54–11.17	0.24
	PS			
	0–1	1.00		
	2–3	4.49	1.15–17.45	0.03
	Stage			
	I, II	1.00		
	III, IV	1.02	0.23–4.45	0.98
	Extranodal sites			
	0–1	1.00		
	≤2	0.70	0.15–3.39	0.66

SIL2R, soluble interleukin-2 receptor; IPI, International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; HR, hazard ratio; CI, confidential interval; EFS, event-free survival; PS, performance status; OS, overall survival; LDH, lactate dehydrogenase; RCHOP, rituximab-combined CHOP.

Table 5. Multivariate Cox proportional hazard analysis for SIL-2R and categorized IPI in both treatment groups

	Variables	HR	95% CI	*P* value
CHOP				
EFS	SIL-2R			
	Low	1.00		
	High	2.98	1.22–7.29	0.01
	IPI			
	L/L-I	1.00		
	H/H-I	2.47	1.11–5.47	0.02
OS	SIL-2R			
	Low	1.00		
	High	3.12	0.93–10.41	0.06
	IPI			
	L/L-I	1.00		
	H/H-I	4.66	1.60–13.58	0.005
RCHOP				
EFS	SIL-2R			
	Low	1.00		
	High	3.00	1.12–8.07	0.02
	IPI			
	L/L-I	1.00		
	H/H-I	2.06	0.93–4.57	0.07
OS	SIL-2R			
	Low	1.00		
	High	4.30	0.85–21.91	0.07
	IPI			
	L/L-I	1.00		
	H/H-I	4.16	0.80–6.69	0.08

SIL2R, soluble interleukin-2 receptor; IPI, International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; HR, hazard ratio; CI, confidential interval; EFS, event-free survival; OS, overall survival; LDH, lactate dehydrogenase; RCHOP, rituximab-combined CHOP; L/L-I, low or low-intermediate; H/H-I, high or high-intermediate.

overexpression [24]. BCL6, a marker of germinal center derivation, has been identified as an indicator of favorable outcome in DLBCL [20], although outcome in patients receiving immunochemotherapy was reported to be uninfluenced by BCL6 status [22]. Similarly, no correlation between immunohistochemically defined GC phenotype and survival rate was observed in patients receiving immunochemotherapy [21], in contrast to previous findings of inferior outcomes in non-GC patients relative to GC patients in the prerituximab era [23]. Up to now, no marker other than IPI has been found to be of prognostic relevance since the clinical introduction of rituximab.

The mechanism by which rituximab added to chemotherapy improves outcome in relation to biological features has been evaluated in several studies. They showed that rituximab may suppress the constitutively active nuclear factor-kappa B pathway in non-GC phenotype DLBCL or downregulate Bcl-2-related antiapoptotic proteins, thereby increasing the sensitivity of lymphoma cells to chemotherapy [27–29]. These effects of rituximab may reduce the prognostic significance of the non-GC phenotype and BCL2. Although the mechanism by which SIL-2R retains its prognostic value after addition of rituximab to chemotherapy is unknown, SIL-2R may directly represent the tumor burden [7, 8].

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To date, several studies including the present one have demonstrated that IPI score remains predictive in the rituximab era, in contrast to biomarkers [18, 22, 23]. In the present study, the IPI system identified only two risk groups instead of four among our patients—a low and low-intermediate group and a high and high-intermediate group—as reported in previous studies [22, 23].

The addition of rituximab to chemotherapy has improved the outcome of patients. We and others have shown that OS now exceeds 50% even in the groups with unfavorable indicators [14–18, 22, 23], although some patients still have a very poor outcome. Therefore, other predictive factors must be characterized in order to identify patients who should receive alternative initial therapy. A number of molecular prognostic markers have already been identified in patients with DLBCL [30]. These markers now need to be reevaluated in the rituximab era to identify patients with unfavorable prognostic factors and to devise adequate treatment strategies.

In conclusion, we have demonstrated that a high serum SIL-2R level is an indicator of poor prognosis in DLBCL patients receiving rituximab combination chemotherapy. To accurately confirm whether serum SIL-2R influences the outcome of patients receiving rituximab combination chemotherapy, prospective investigation with long-term follow-up will be required.

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Does Rituximab Really Induce Hepatitis C Virus Reactivation?

TO THE EDITOR: We wish to raise several issues regarding the recent case report by Hsieh et al.[1] Both the title of the article and its conclusion suggest that rituximab-induced reactivation of hepatitis C virus (HCV) is possible during combination chemotherapy with rituximab. We think it cannot be concluded with certainty whether rituximab alone was associated with HCV reactivation in the case described.

The first reason for the authors' conclusion is that liver dysfunction did not develop during initial chemotherapy and occurred after combination chemotherapy with rituximab. However, it is known that HCV-infected patients first develop liver dysfunction after the second or later cycles of chemotherapy. Indeed, a previous study of liver dysfunction in HCV-positive patients with diffuse large B-cell lymphoma treated with a cyclophosphamide, vincristine, doxorubicin, and prednisolone–like regimen has shown that the incidence of hepatic toxicity tended to increase with the number of chemotherapy courses.[2]

Reactivation of viruses such as hepatitis B virus (HBV),[3] cytomegalovirus,[4] and varicella-zoster virus[5] is considered to be associated with immunosuppression caused by rituximab treatment. Rituximab targets and depletes CD20-positive malignant lymphocytes along with normal CD20-positive B cells, and previous studies have demonstrated rapid depletion of normal B lymphocytes, whereas immunoglobulin levels remain within normal limits until at least 6 months after treatment.[6] Indeed, HBV reactivation during the fourth to sixth (or between the third and fifth) cycles of rituximab treatment has been reported,[3] and one study has documented markedly late HBV reactivation at several months after completion of rituximab treatment.[7] Therefore we think it is too speculative to conclude that rituximab was responsible for the rapid increase of transaminase levels during the clinical course described.

It is difficult to determine whether liver dysfunction is caused by HCV reactivation or chemotherapy toxicity. In fulminant hepatitis caused by HCV reactivation, the level of HCV RNA has been reported to increase during chemotherapy and dramatically decrease at the onset of severe liver dysfunction.[8] In fact, we have experienced a case in which the expression of HCV RNA increased during rituximab chemotherapy and dramatically decreased to below the normal limit at the time of severe liver dysfunction.[9] The changes in serum HCV RNA and transaminase levels described in the latter two reports suggest that the liver dysfunction may have been caused by the spread of HCV in the liver and the resulting immune reaction against HCV-infected hepatocytes. However, for the patient described, the authors provide no data to suggest HCV viral load before and after liver dysfunction.

The authors also consider that a synchronized increase of HCV RNA and transaminases could have accounted for the rituximab-induced HCV reactivation. However, they present no details of HCV RNA levels during the first course of chemotherapy without rituximab, and it is unclear whether the HCV viral load had increased before rituximab administration. A previous study of nine patients with chronic HCV hepatitis has shown that prednisone therapy increased the HCV RNA level in all of them,[10] suggesting that anticancer agents may have induced the increase of HCV RNA. Therefore, we think that, in this particular case, it is necessary to clarify how the HCV RNA level changed during the course of treatment.

Liver dysfunction during rituximab-containing chemotherapy needs additional investigation, given that rituximab-induced HBV reactivation is a significant clinical problem. If rituximab did, in fact induce severe liver dysfunction through HCV reactivation in the present case, this would have important implications for clinical management. Additional detailed information on the association between rituximab infusion and HCV reactivation is therefore required.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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がん治療
実践研修プログラム

大腸

財団法人癌研究会有明病院化学療法科

この資料は厚生労働省がん臨床研究事業「外来化学療法における部門の体制および有害事象発生時の対応と安全管理システムに関する研究」の研究費より印刷しております。

H20−がん臨床−一般−006　畠 清彦班

参考資料1

がん治療実践研修プログラム

大腸

がん治療実践研修プログラム

癌研有明病院化学療法科・血液腫瘍科
外来治療センター
畠清彦

目標

- 大腸癌・乳癌の戦略的化学療法を学ぶ
  - 治療についても学ぶ：見学と説明文書作成実習
  - 有害事象の観察と対応
- チーム医療の構築
- 近未来の治療導入の仮想的練習
- 一方で研修後に近くの施設を集めて研修が開催できる
- どういう病院なのかをアピールできる

研修予定内容

- **FOLFOX6療法とXELOX療法（+Bev）**
- アービータックス
- **Paclitaxel+Herceptin**
- **RCHOP療法、bortezomib療法**
- など多くの実地に導入されるべき治療方法の実際を学んで、帰ってからすぐに実行できる。
- 注射による抗癌剤の治療を正しく普及させる

大腸プログラム

	月曜日	火曜日	水曜日	木曜日	金曜日
9時	[illegible]	ポート見学	病棟 [illegible]	病棟 [illegible]	乳腺カンファ（8時から）
10時	見学スタート	ポート見学	ASCO-GIの最新トピックス	[illegible]	[illegible]
11時		ポートワークショップ			
12時	病棟カンファ		血液カンファ	血液カンファ	
13時	病棟カンファ	アービータックス講義			
14時		アービータックス講義	病棟カンファ（ナースから）	[illegible]	
15時	消化器グループカンファ		[illegible]	薬剤部・ミキシング	書類のチェック
16時	ポート＆FOLFOX（[illegible]）	ATC見学	[illegible]に関する講義		書類のチェック
17時	ポート講義		17:00 [illegible]カンファ	[illegible]	書類のチェック
18時		18:40大腸癌カンファランス（[illegible]のみ）	消化器カンファ・FOLFOX有害事象レビュー	消化器[illegible]・カンファ	
19時以降				薬剤部[illegible]	

＊スケジュールは変更されることがあります

乳癌プログラム

（ Paclitaxel+Herceptinの場合またはvinorelbine+Herceptin ）

時間	火	水	木
8-9	/	病棟カンファ	病棟カンファ
9-10	/	外来	ATC見学
10-11	/	外来	文書作成
11-12	/	外来	文書作成
12-13	昼食	12:15-13:30 血液カンファ	12:15-13:30 血液カンファ
13-14	回診	化学療法講義	
14-15	回診	生殖機能の保護について	文書チェック
15-16	乳癌講義	パクリタキセル＋ハーセプチン	[illegible]
16-17	パクリタキセル＋ハーセプチン		[illegible]
17-18		[illegible]	
19-		[illegible]	

＊スケジュールは変更される場合があります

学習目標

- 自分の現在の病院、科の評価と反省
- 問題点といかにしたら導入できるのかを具体的に解決方法を、発表する
- 3職種で解決していく
- 癌研有明病院の資料から自分の施設用の説明文書や他のひとへの学習材料を作成する
- 次に併用されるべき薬剤の情報を得て帰る

個々の目標は異なるがハーモニーが重要である

- 医師：リーダーシップ、抗がん剤の作用機序と併用療法の理解、IC,　有害事象対処、外来治療の利点の理解、効率的外来運用
- 看護師：有害事象の理解、有害事象観察、入院中に患者セルフケア能力を向上、ICのサポート、緊急連絡時の説明、コストの説明
- 薬剤師：服薬指導、薬剤の説明、有害事象説明、ミキシング、dose intensityのチェック、durationのチェック、禁忌など
- 見える化、伝える化へ

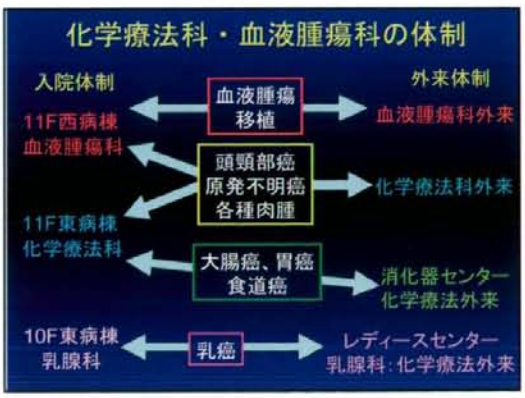
チーム医療をつくるには？

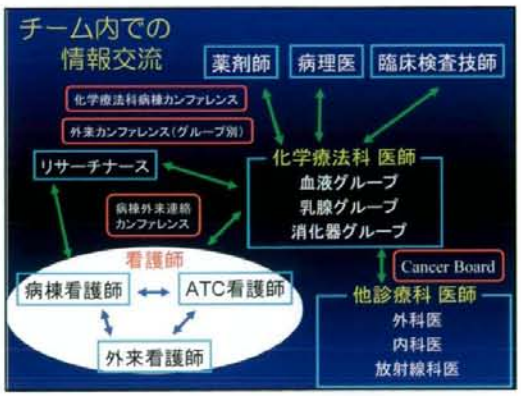
- チームのメンバー
- 医師
- 薬剤師
- 看護師
- 検査技師
- 医事課職員

- できたかどうかは何でみる？
- カンファレンス
- 治療法の統一
- インシデントアクシデントレポート
- 患者の成績向上、感謝
- 病院のレベル向上
- 患者数増加、収入増加

作成する資材など

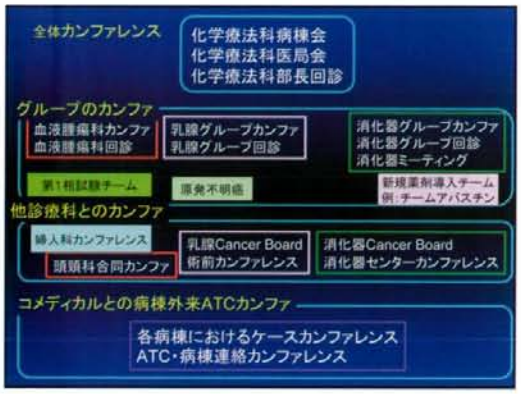
- 患者教育、看護師教育、薬剤師の患者説明（服薬指導など）
- 同意書、薬物療法同意書、化学療法ごとの説明文書、有害事象説明
- コストに関する同意書

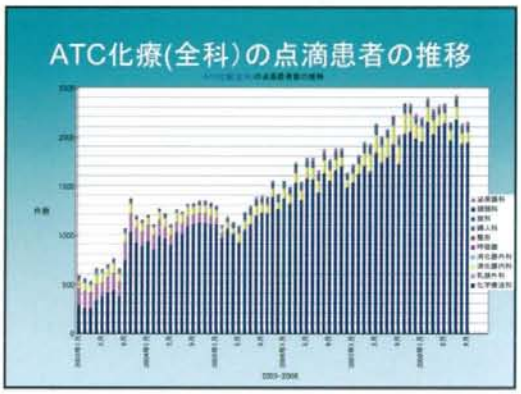




月曜	昼：化学療法科病棟会、部長回診
火曜	昼：乳腺グループカンファレンス 乳腺グループ回診
水曜	昼：血液腫瘍科カンファレンス 夜：頭頸科合同カンファ 化学療法科医局会
木曜	昼：血液腫瘍科カンファレンス 夜：消化器グループカンファレンス 消化器グループ回診
金曜	昼：乳腺グループカンファレンス 夜：消化器グループミーティング
土曜	朝：病棟・外来・ATC連絡会

昼食の時間を利用して！
集まりが良い時間帯に！





年別 新患患者数

外科医からの紹介がスムーズに行われており、増加している

	乳癌	血液	大腸	食道	胃	その他	計
2000年	241	70	11			20	342
2001年	282	160	57	5	7		511
2002年	284	148	135	155	110		832
2003年	317	133	131	94	72	175	922
2004年	481	209	204	97	110	50	1151
2005年	484	273	298	84	176	103	1418
2006年	748	353	579	136	358	352	2526
2007年	63	28	42	14	32	30	209

実際のがん拠点病院ではどうか？

- 病病連携
- 地域連携
- 外来治療と緊急体制
- 緩和ケア症例の扱い
- セカンドオピニオン
- がん医療相談窓口
- 精神腫瘍科
- チーム医療

欠けているのは真のリーダーシップ

- チーム医療形成はできるが、教育には時間と手間がかかる

- なにを手伝えるのか？
- 看護師教育
- 薬剤師指導
- 患者向け資材作成指導

がん薬物療法専門医を目指す先生方へのメッセージ
Medical oncologistが行うべき対応

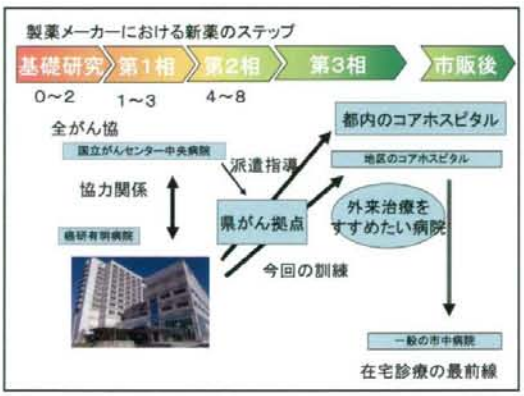
- 各種分子標的薬剤の有害事象を理解する
- 有害事象へのすばやい、適切な対応を
- できないときは、ほかの専門医と協調して安全な体制を作る
- 救急医、画像診断医、呼吸器内科医、循環器内科医、血管外科医など
- チーム医療はもちろんだが、自分の科内部での情報共有、各科専門医との協調が重要
- 予測して当たることが重要

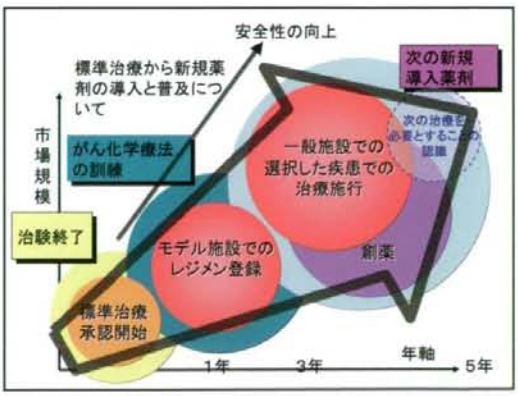
余裕があったら

- 自分たちで自習で説明文書を作成していく
- 説明の練習、ﾌﾟﾚｾﾞﾝﾃｰｼｮﾝの練習と準備
- 他の施設、他の職種にわかるように説明する
- それでも余裕があるなら、胃癌や食道がん、大腸がんも学ぶ

準備しておく知識

1. 分子標的治療薬に特徴的な有害事象
   - Herceptin
   - Avastin
   - Rituxan
   - Glivec
   - Iressa
   - Velcade
   - Mylotarg
2. 有害事象マネージメントにおけるチーム医療の重要性





分子標的治療薬：種類

<モノクローナル抗体>

製品名	一般名	標的	適応疾患
Herceptin	Trastuzumab	HER2	BC
Avastin	Bevacizumab	VEGF	CRC
Rituxan	Rituximab	CD20	NHL
Mylotarg	Gemtuzumab ozogamicin	CD33	AML
Erbitux	Cetuximab	EGFR	CRC
Vectivix	Panitumumab	EGFR	CRC
Zevalin	Ibritumomab Tiuxetan	CD20	NHL

<低分子化合物>

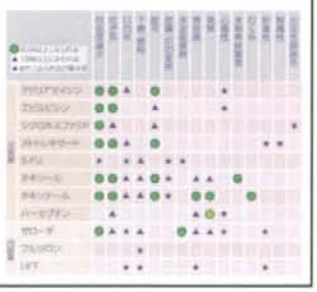
製品名	一般名	標的	適応疾患
Glivec	Imatinib mesilate	Bcr-Abl	CML GIST
Iressa	Gefitinib	EGFR	NSCLC
Velcade	Bortezomib	Proteasome	MM
Tarceva	Erlotinib	EGFR	NSCLC
Nexavar	Sorafenib	Multiple RTKs (CRAF, BRAF, KIT, VEGFR etc)	RCC
Sutent	Sunitinib malate	Multiple RTKs (PDFR, VEGFR etc)	RCC
Tykerb	Lapatinib	EGFR, HER2	BC

分子標的治療薬：がん腫毎

Disease	Molecular targeting agent	Target
乳癌	ハーセプチン	HER2
	Lapatinib	*HER2*
	Bevacizumab	*VEGF*
大腸癌	アバスチン	VEGF
	Cetuximab	*EGFR*
	Panitumumab	*EGFR*
肺癌	イレッサ	EGFR
	Erlotinib	*EGFR*
	Bevacizumab	*VEGF*
悪性リンパ腫	リツキサン	CD20
	Ibritumomab tiuxetan	*CD20*
	Bortezomib	*Proteasome*
多発性骨髄腫	ベルケード	Proteasome

化学療法共通の有害事象

- 好中球減少
- 血小板減少
- 粘膜障害
- 手足症候群
- 嘔気・嘔吐
- 倦怠感
- 過敏症



心毒性，肺毒性

心毒性
- Doxorubicin
- Cyclophosphamide (in high doses)
- Mitoxantrone
- Busulfan
- Mitomycin C
- Taxol
- 5-FU

肺毒性
- Bleomycin
- Cycrophosphamide(rare)
- Gemcitabine (w/prior XRT)
- Vinorelbine
- MTX
- Mitomycin C

ハーセプチンの使用成績調査より

- 目的
  使用実態下における副作用の発生状況、未知の副作用、安全性・有効性に影響を与えると考えられる要因および有効性を把握すること
- 対象症例
  -契約締結施設にて登録期間中に症例登録を行い、ハーセプチンを使用した
  -全症例
- 治療方法
  使用実態下の調査であるため、用法・用量については特に定めない
- 登録期間
  平成13年6月～平成13年11月（6ヶ月間）
- 調査期間
  平成13年6月～平成14年3月
- 安全性集計対象
  1142例

ハーセプチン

副作用 発現状況（全体）

副作用発現率

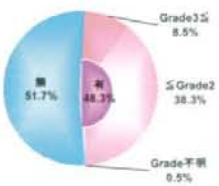
48.3% （552 / 1,142例）

副作用発現件数：1,131件

<重篤度別（厚生労働省 重篤定義）>

重篤： 7.5% （86 /1,142例）

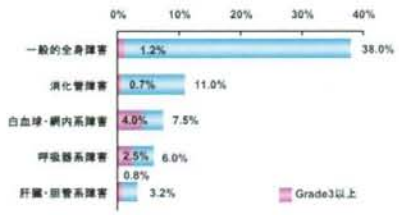
非重篤： 40.8% （466 /1,142例）



ハーセプチン

副作用発現状況

＜主な副作用（器官分類別）＞



ハーセプチン

副作用発現状況

＜主な副作用（種類別）＞

ハーセプチン

心障害

1．症状

主としてうっ血性心不全

心不全：症候：呼吸困難、起座呼吸、咳増加等
　　症状・異常：S3ギャロップ、駆出率低下、末梢性浮腫等
その他：心筋症、徐脈、心膜炎、心嚢液貯留、肺浮腫、心原性ショック等

2．心機能検査

検査方法*：心エコー（必須）
検査時期の目安**：
・投与前（必須）
・投与開始後　通常：3ヶ月毎　無症候性心機能障害：6～8週毎
心症状の発現状況・症状に応じて頻回に実施。
患者の状態（心駆出率の変動を含む）を十分に観察する

*本剤投与による心機能障害の発現機構の把握は、心電図では不十分であり、心エコー検査やMUGAスキャンによる「心駆出率（EF：Ejection Fraction）」の測定が必要です。
**EU添付文書より

心毒性の予防と早期発見で最も重要なのは、心機能のモニタリングです。

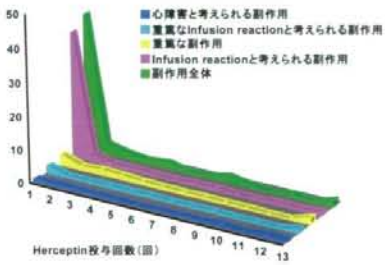
治療開始前には、すべての症例で理学的所見、心電図、心エコーなどで心機能を評価します。高リスク患者に心毒性の発現頻度の高い抗がん剤を投与する場合には、定期的なモニタリングを行って早期発見に努めます。

表15 早期診断のための心機能モニタリング

- **胸部X線**　→ **心拡大、肺うっ血に注意**
- **心電図**　→ **QRSの低電位化、QTcの延長、ST-T変化に注意**
- **ホルター心電図** → **ST-T変化に注意**
- **心エコー**　→ **左室駆出率（EF）の10%以上の低下または50%以下に低下した場合は、投与中止を検討**
- RIアンギオグラフィ
  - **心プールシンチ、MIBG心筋シンチ**
- **バイオマーカー**
  - **BNP、トロポニンなど**

ハーセプチン

副作用発現までの投与回数



Infusion reaction

■ 各抗体製剤における発現頻度

- リツキサン　約90%
- ハーセプチン　約40%
- マイロターグ　50%以上
- アバスチン　まれ

Infusion reaction: リツキサン-1

投与に関連して投与中から開始後24時間以内に多く発現する副作用

■主な症状：発熱、悪寒、悪心、頭痛、疼痛、そう痒、発疹、咳、虚脱感、血管浮腫等
これらの症状は通常軽微～中等度
国内臨床第Ⅱ相試験で、初回投与時約90%の症例に発現

■重篤な症状： アナフィラキシー様症状、肺障害、心障害等
死亡例が報告されている
【低血圧、血管浮腫、低酸素血症、気管支痙攣、肺炎（間質性肺炎、急性呼 アレルギー性肺炎等を含む）、閉塞性細気管支炎、肺浸潤、吸促迫症候群、心筋梗塞、心室細動、心原性ショック等】

Infusion reaction: リツキサン-2

■注意を要する患者
- 血液中に大量の腫瘍細胞がある(25,000/μL以上)など腫瘍量の多い患者
- 肺腫を伴う患者
- 心機能、肺機能障害を有する患者

■観察項目
- 投与中はバイタルサインのモニタリングや自他覚症状の観察を行う。
- 投与後も患者の状態を十分観察する。

■対処方法
＜軽微～中等度の場合＞
・患者の状態を十分に観察し、必要に応じて対症療法を行う。
（解熱鎮痛剤、抗ヒスタミン剤の投与等）
・注入速度を緩めるか、投与を中断することも考慮する。
＜重篤な場合＞
・直ちに投与を中止し適切な処置を行う。
（酸素吸入、昇圧剤、気管支拡張剤、副腎皮質ホルモン剤の投与等）

腫瘍崩壊症候群：リツキサン

治療などにより腫瘍細胞の急速な崩壊が起こる結果、大量の核酸、リン酸、カリウムが細胞内より血中に放出され、致命的な電解質異常および尿酸やリン酸カルシウムの析出による重篤な腎不全が生じること。

■症状
- 腎不全、高カリウム血症、低カルシウム血症、高尿酸血症、高Al-P血症等

■注意を要する患者
- 血液中に大量の腫瘍細胞がある患者、脱水・腎機能障害のある患者

■発現時期
- 初回投与後12～24時間以内に多くあらわれる。

■予防
- 高尿酸血症治療剤（アロプリノール等）の投与
- 補液による尿量の確保

■対処方法
- 点滴中にあらわれた場合は直ちに投与を中止する。
- 適切な処置を行う。（生理食塩液、高尿酸血症治療剤等の投与、透析等）
- 症状が回復するまで患者の状態を十分に観察する。

リツキサン使用成績調査より

リツキサン使用成績調査：副作用発現状況-1

◇ 副作用発現症例数および副作用分類別の発現症例数

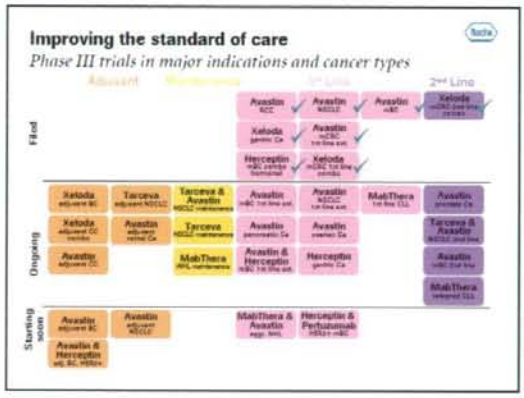
副作用種類	発現症例数	（重篤）	発現頻度	（重篤例頻度）
全副作用	583	(186)	51.3%	(16.4%)
血液毒性（単剤治療：146 例）	24	(5)	16.4%	(3.4%)
血液毒性（化学療法併用：991例）	299	(133)	30.2%	(13.4%)
臨床検査値異常	119	(2)	10.5%	(0.2%)
非血液毒性	446	(63)	39.2%	(5.5%)

■ 重篤 ■ 非重篤

Bevacizumab/ Avastin

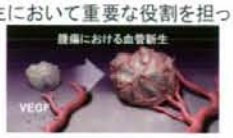
遺伝子組換えヒト化 抗VEGFモノクローナル抗体
（マウス抗ヒトVEGF抗体A4.6.1由来）

- 一般名：ベバシズマブ（遺伝子組換え）
- 分子量：約149,000 Da
- 由来：93% ヒトIgG1由来、7% マウス由来
- 構造：アミノ酸214個の軽鎖2分子とアミノ酸453個の重鎖2分子からなる糖たん白質
- 標的：ヒトVEGF（VEGF-A）の全アイソフォームに結合し、VEGFの生物活性を中和
- 親和性：マウスA4.6.1抗体と同等のVEGF親和性
- 種特異性：本抗VEGF抗体の結合は、ヒト、霊長類、ウサギのVEGFに限定される



アバスチン：標的VEGFについて

- 脈管形成および血管新生において重要な役割を担っている有力な因子のひとつ



- 胚形成や出生後早期の発育、骨格の成長、黄体形成の成熟・ 子宮の血管形成、創傷治癒に関わっている因子

腫瘍特異的な
血管新生阻害ではない

アバスチン：主な有害事象

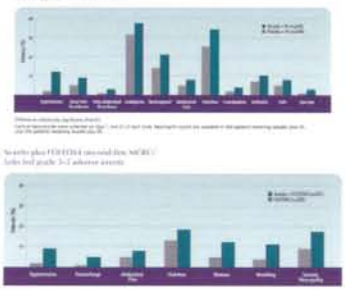
海外調査研究（1,914例、41カ国）での結果

	Any AE or SAE N(%) (n=1,914)	CTC grade 3-5 or SAE N(%) (n=1,914)
高血圧	508(26.5)	88(4.6)*
たん白尿	168(8.8)†	13(0.7)*
出血	557(29.1)	50(2.6)
創傷治癒	67(3.5)	20(1.0)*
動脈血栓塞栓症	23(1.2)	22(1.1)
消化管穿孔	33(1.7)‡	33(1.7)

*No fatal events; † At baseline, 8.8% reported CTC grade 1/ 2 and 0.1% grade 3/ 4 proteinuria.
‡ One patient hospitalised for microperforation

E. Van Cutsem, et al., ASCO-GI 2007, abst 346, First BEAT Trial

アバスチンAes：海外臨床試験



動脈血栓塞栓症

- Angina：狭心症
- Myocardial infarction：心筋梗塞
- Transient ischemic attack ：過性虚血発作
- Cerebral infarction：脳梗塞
- Peripheral embolus：末梢塞栓

消化管穿孔GI perforation

- 全頻度Overall incidence in CRC 1.7%
- 初発切除例Primary resected 1.6%
- 初発Primary intact 2.6%
- In MBC 0.4%
- In NSCLC 0.8%

- Time to perforation: 2.1 months
- Unrelated to: PUD, ASA, NSAID, diverticulosis
- Possibly related to: RT, p. carcinomatosis, abscess GI obstruction or acute diverticulitis

出血: 頻度 grade 3–4

大腸がん	0.6% to 2.1%
NSCLC	3% to 15%
転移性乳癌	0.4% to 1.5%

アバスチン治療前にmajor surgeryを行ったmCRCでのWound healing/ bleeding

	IFL + placebo	IFL + bevacizumab
Major surgery 28–60 days prior to therapy	1/155	3/150

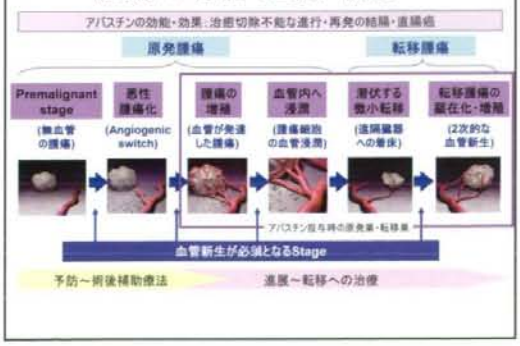
Scappaticci F, et al. J Surg Oncol 2005;91:173–80

Bevacizumab safety summary

	CRC	NSCLC	BC
1. HTN, proteinuria and epistaxis	X	X	X
2. GI perforation and wound healing	X		
3. ATE	X		
4. Bleeding	X	X	

腫瘍増殖過程から見たアバスチンの投与とその根拠

腫瘍の増殖・進展・転移



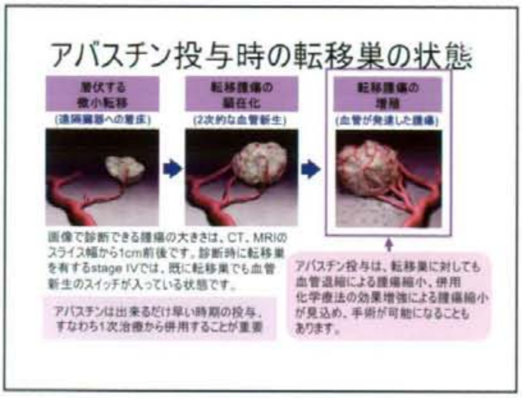
アバスチン投与時の原発巣の状態

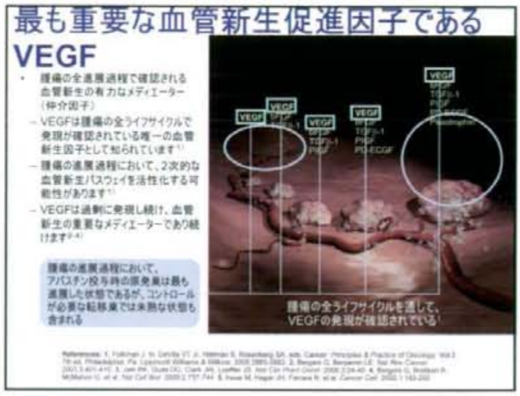
本邦では化学療法を開始する前に原発巣を切除するのが一般的です

初診時：stage IV（治癒切除不能）

Stage IVであるので、既に転移巣が存在しています。
原発腫瘍はVEGFを産生して、継続的に増殖するとともに、腫瘍細胞は血管に浸潤し血流に乗って肝臓や肺などの遠隔臓器に転移しています。

この状態でアバスチンを投与すると、血管の退縮による原発巣の縮小、併用化学療法の効果増強による原発巣の縮小、新たな血管の新生を抑制することによる新たな転移の抑制が見込めます。

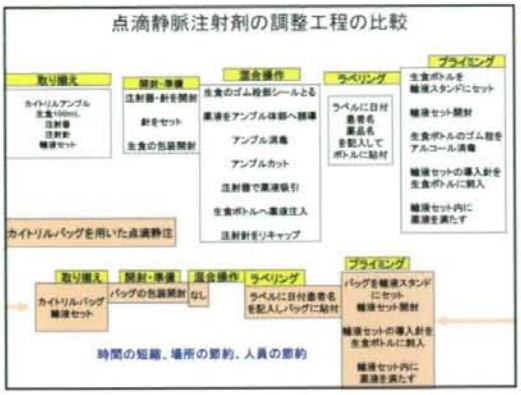


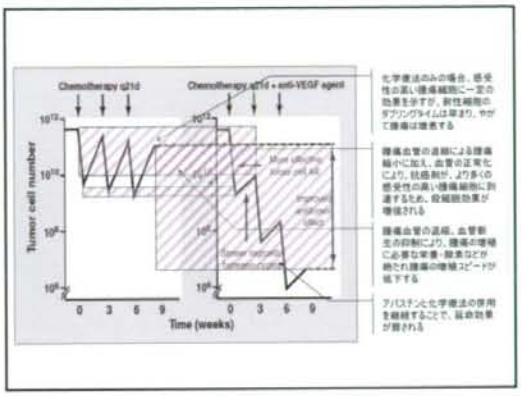


大腸癌で標準治療が変化すると?

	必要時間	奏効率	TTP	比率/回	時間XTTP
Xeloda	0	29			
5-FU/LV	0.5	20	9	1	1
CPT-11	1.5	20	9	3	
IFL	2	35	12	4	6
FOLFOX4	2.5	40	14	5	7.5
FL+B	1.5	30	14	3	4.5
FOLFOX+BV	4	50	20	8	16
Xelox	2	40	14	4	8
Xelox+BV	3	50	20	6	12

外来への負担、外来医への負担、ATCへの負担





マイロターグ：肝SOSのマネージメント

- Determining the cause of liver dysfunction
- Identifying the cause of jaundice
- Evaluation of painful hematomegaly
- Evaluation of ascites
- Evaluation of elevations of serum GOT/GPT
- Evaluation of nonhepatic conditions that contribute to jaundice
- Liver biopsy and measurement of sinusoidal pressure

Medical care of patients with SOS

- Maintain liver blood flow
- Minimize extravascular fluid accumulation
- Avoidance of further hepatic injury
- Prevention of bacterial translocation
- Prevention of viral and fungal infection

McDonald GB, Clinical Lymphoma 2(suppl1)S35-39, 2002

EGFR/HERファミリーと分子標的治療薬