表1　前立腺のリスク分類

Risk Scoring			
	Seattle[2]	Mt. Sinai[3]	D'Amico[4]
Low	iPSA≦10 GS 2-6 StageT1a-T2b	iPSA≦10 GS 2-6 StageT1a-T2a	iPSA≦10 GS 2-6 StageT1c-T2a
Intermediate	iPSA>10 or GS≧7 or Stage≧T2c	iPSA=10.1-20 or GS 7 or StageT2b	iPSA=10.1-20 and/or GS 7 and/or StageT2b
High	2 or 3 intermediate risk factors	2 or 3 intermediate risk factors or iPSA>20 GS 8-10 or Stage≧T2c	iPSA>20 and/or GS 8-10 StageT2c

外照射によるRTOG第III相試験症例によるリスク分類[5]					
Risk Group	T-Stage	Node Status	Gleason Score	Disease-Specific Survival 5-yr	10-yr	15-yr
1	T1-2	Nx	2-6	96%	86%	72%
2	T1-2	Nx	7	94%	75%	61%
	T3	Nx	2-6			
	T1-3	N+	2-6			
3	T1-2	Nx	8-10	83%	62%	39%
	T3	Nx	7			
	T1-3	N+	7			
4	T3	Nx	8-10	64%	34%	27%
	T1-3	N+	8-10			

iPSA=initial prostate specific antigen
GS= Gleason score

表2　リスク分類と治療方法による5年PSA無再発生存率[2]

Treatment	Seattle Risk Group		
	Low	Intermediate	High
3D-CRT; Zelefsky[6] (, 2001)	90%	70%	47%
Seeds; Blasko[7] (Seattle, 2000)	94%	82%	65%
Seeds+EBRT; Sylvester[8] (, 2002)	85%	77%	45%
Radical Prostatectomy; D'Amico[9] (Univ. Pennsylvania, 2000)	85%	65%	32%
Radical Prostatectomy; D'Amico[9] (B&W, 2000)	83%	50%	28%
Radical Prostatectomy; Kupelian[9] (Cleveland, 1997)	81%	40%	—

前立腺周囲には直腸や膀胱などリスク臓器が隣接しており，従来の放射線治療 (Conventional Radiotherapy) では腫瘍に対する高線量の投与は困難であった。そこで治療成績の向上と有害事象の軽減を目指し，さまざまな放射線治療技術が開発されてきた。本邦では高橋らにより開発された原体照射が以前より応用されており，さらに三次元原体放射線治療 (Three-dimensional conformal radiotherapy; 3D-CRT) が普及してきた。原体照射とは，森田らによれば“光子線ないし粒子線ビームを用いた二次元ないし三次元方向からの回転運動照射で，どの照射方向から見ても照射野形状がターゲット形状に一致している照射法”とされている[13]。最近ではCT-simulator，治療計画装置，照射野形状を作成するためのマルチリーフコリメーター (Multi-leaf Collimator; MLC) を搭載した治療装置とネットワークの構築によりさらに複雑な3D-CRTが可能となっている。

3D-CRTとは永田らによれば[14]，“薄い間隔で撮像された複数のCT画像に基づいて，正確なターゲット領域とリスク臓器の幾何学的配置を決定し，それらを画像処理した種々の三次元画像を用いたうえで，適切な三次元線量計算に基づく正確な放射線治療計画”とされる。従来の放射線治療が“照射方向と照射野辺縁の設定をしてからターゲット内の線量分布を確認する”のに対し，“ターゲットと関連正常臓器の輪郭を設定してから，計算された三次元画像を利用することによって，照射方向や照射門数を決定する”ように，治療計画は大きな変化を遂げた。さらに，強度変調放射線治療 (Intensity-Modulated Radiotherapy; IMRT) では“ターゲットの内部の詳細な照射線量と各種関連リスク臓器の詳細な容積線量を定義 (prescribe) した後に，治療計画装置によって最適な照射方法を決定する”こととなり，望ましい線量分布の実現が治療計画装置の進歩により可能となりつつある。治療計画の選択においては，従来治療計画を行って線量分布を計算し (forward planning),

表3　外照射による前立腺がんに対するDose Escalation Study

Author	No.	Subset of Pt.	Dose	Local Control	p-value	Biochemical Control	p-value	Cause-specific Survival rate	p-value	Overall Survival rate	p-value
Kupelian[15] (Cleveland)	1041	All subsets	≧72 Gy <72 Gy	95%/8-yr 83%/8-yr	0.026	87%/8-yr 51%/8-yr	<0.001				
Shipley[16] (Harvard)	202	T3-4, poorly diff.	75.6 Gy 67.2 Gy	84%/8-yr 19%/8-yr	0.0014			67%/8-yr 62%/8-yr	NS	55%/8-yr 51%/8-yr	NS
Valicenti[17] (RTOG)	1465	GS 8-10	>66 Gy ≦66 Gy	78%/5-yr 66%/5-yr	0.076			46%/10-yr 31%/10-yr	<0.05	27%/10-yr 18%/10-yr	<0.05
Zelefsky[18] (Memorial Sloan-Kettering C.C.)	828	T1-3	75.6 Gy 70.2 Gy <70.2 Gy	Favolable 75.6 Gy:83%/10-yr <70.2 Gy:57%/10-yr Intermediate 75.6Gy:50%/10-yr <70.2 Gy:42%/10-yr Unfavolable 75.6Gy:42%/10-yr <70.2 Gy:24%/10-yr	p=0.003 p=0.05 p=0.04						
Hanks[19] (Fox Chase C.C.)	714	GS 7-10	≧74Gy <74Gy					100%/5-yr 89%/5-yr	0.029	88%/5-yr 78%/5-yr	NS
		T2c-T3	≧74Gy <74Gy					95%/5-yr 87%/5-yr	NS	88%/5-yr 73%/5-yr	0.039
Pollack[20] (M. D. Anderson C.C.)	301	T1-3	78 Gy 70 Gy			70%/6-yr 64%/6-yr	p=0.03				

その比較により最適治療計画を選択していたが，IMRTによって線量を設定したあとに治療計画を最適化するinversed planningが実現している。IMRTは総線量増加を目的とした臨床試験において，近年さかんに前立腺がんに応用されている。治療計画の比較には，線量分布図以外に容積線量ヒストグラム (Dose-Volume Histogram; DVH) が使用され，ターゲットや周囲の重要なリスク臓器の全容積中の照射線量が表示されている。TCP (tumor control probability) やNTCP (normal tissue complication probability) の計算も可能である。

前立腺がんにおいては総線量の増加により，局所制御率やPSA無再発生存率が向上することが示されている。表3に外照射によるDose escalation studyの結果を示す。Zelefskyらの Memorial Sloan-Kettering Cancer Centerにおける828症例の検討によると[18]，10年PSA無再発生存率はFavolable・Intermediate・Unfavolable riskの各々で70.2Gy未満に比較し75.6Gyで良好であった。Pollackらによる M. D. Anderson Cancer Centerの報告では[20]，T1-3症例に対する第Ⅲ相比較試験の結果，6年PSA無再発率は70Gy群で64%に対し78 Gy群で70%と有意差を認めていた (p=0.03)。特に治療前のPSAが＞10ng/mlの症例では6年PSA無再発率は70Gy群で43%に対し78Gy群では62%と良好であった (p=0.01)。6年後のGrade2以上の直腸の遅発性放射線反応は，70Gy群で12%に対し78Gy群で26%と78Gy群で有意に多く認められており注意が必要である (p= 0.001)。膀胱の遅発性放射線反応は，両群で10%であり差がなかった。現在RTOGでは3D-CRTによる72.93Gyと82.28Gyの第Ⅲ相比較試験 (RTOG P-0126) を施行中であり，結果が注目される。

2．粒子線治療

粒子線治療は腫瘍制御率の向上と周囲正常組織の有害反応軽減を目的として，前立腺がん治療に利用されてきた。陽子線や重粒子線は物理的特徴としてBragg peakを有し，線量のpeak-plateau ratioが高いために線量分布に優れる。この特徴を応用し周囲正常組織に対する影響を増加せずに前立腺の総線量の増加を図ることが可能となると考えられる。放射線医学総合研究所重粒子治療センターでは重粒子線の1つである炭素線を用いて，1995年より前立腺がんに対する臨床研究が開始されている。第I/II相試験の結果，その後の第II相試験では炭素線治療66GyEを行っている。

陽子線治療ではMassachusetts General Hospitalにおいて1970年代より前立腺がんに対する陽子線治療が開始された。Loma Linda大学では1991

年より局所進行前立腺がんに対して陽子線ブースト照射を用いた治療を行っている。X線照射45Gyと陽子線ブースト照射30GyEを行い5年生存率89%，5年生化学的無病生存率79%と良好な成績を報告している[21]。日本においては，筑波大学陽子線医学利用センターにおいて1985年より前立腺がんに対する陽子線治療が行われ，国立がんセンター東病院では2001年より病院設置型陽子線治療装置による前立腺がんの治療が開始されている。多施設共同臨床試験としては，アメリカでProton Radiation Oncology Group (PROG) が，早期前立腺がん (T1b-T2b, PSA ≦ 15) に対し70.2GyEと79.2GyEの第Ⅲ相比較試験を行っており，本邦でもT1b-T3bN0M0を対象とする多施設共同第Ⅱ相試験が計画されており，今後の成果が期待されている。

3．組織内照射

前立腺がんに対する組織内照射には^{125}Iや^{103}Pd等の核種を密封したシード線源による永久挿入密封小線源治療や低線量率^{192}Ir線源による一時装着法，高線量率^{192}Ir線源による高線量率組織内照射がある（表4）。永久挿入密封小線源治療は限局性の前立腺がんの中，特にLow Risk群で以前より欧米では広く応用されてきた。古くは1914年に^{226}Raを用いた報告があるが[31]，1980年代より経直腸的超音波ガイドによるアプローチにより発展を遂げリアルタイムに三次元的表示が可能となった。アメリカでは標準的治療の一環として1998年には23,000件が施行され，症例の増加により年間50,000件以上の実施が想定されている。表3に^{125}Iや^{103}Pdでの永久挿入密封小線源治療単独治療および外照射との併用による治療成績を示す。

日本では，厚生労働省の定める「診療用放射線照射器具を永久的に挿入された患者の退出について」平成15年3月3日医薬安第0313001号通知および「患者に永久的に挿入された診療用放射線照射器具（ヨウ素125シード，金198グレイン）の取扱いについて」平成15年7月15日医政指発第0715002号が出され，^{125}Iシード線源の供給が開始されたことにより永久挿入密封小線源治療は標準治療の選択肢の一つとして普及することが予想される。日本放射線腫瘍学会・日本泌尿器科学会・日本医学放射線学会では「シード線源による前立腺永久挿入密封小線源治療の安全管理に関するガイドライン」を作成し，安全性の確保と放射線治療の質の向上を目指している。^{125}Iシードは，軌道電子捕獲により崩壊し平均エネルギーは28.5keVと低く，半減期は59.4日であり周囲への正常組織への影響を低く抑えることが可能である。

American Brachytherapy Society (ABS) は1999年に発表した前立腺永久挿入密封小線源治療に関する勧告のなかで[32]，単独治療の場合は①T1-T2aで，②Gleason sum 2-6かつ，③PSA＜10ng/mlという選択基準を示している。また，外照射に加え追加治療として行うべき症例としては，①T2b, T2cまたは，②Gleason sum 8-10または，③PSA＞20ng/mlという選択基準を示している。会陰浸潤例や生検で陽性多数である場合，両葉で陽性であった症例およびMRI上被膜浸潤が陽性の症例では外照射のboostとしての前立腺永久挿入密封小線源治療の選択を勧めている。さらに，前立腺体積が60cc以上の症例ではホルモン療法による体積の減少後に検討されるべきである。臨床的除外基準としては，期待寿命5年未満の症例やTURPによる大きな，または治癒前の欠損のある症例，施術に関する危険の高い症例および遠隔転移症例を挙げている。また合併症のリスクの高い症例として，大きな中葉，骨盤既照射例，AUA Scoreの高い症例，骨盤内手術の回数が多い症例および重症糖尿病症例が指摘されている。また，TURPの既往，前立腺体積が60cc以上の症例，大きな中葉，精嚢が生検陽性の症例で技術的に十分な照射が困難であると述べている。1995年にAmerican

表4　前立腺永久挿入密封小線源治療症例のPSA

	No.	Treatment	T Stage	Definition	Follow-up	PSA Outcome by Pretreatment PSA			
						0～4	4～10	10～20	20～
Beyer (1997)[22]	489	I-125	T1-2	≧4.0	5 yr	93 %	72 %	42 %	38 %
Blasko (2000)[7]	230	Pd-103	T1-2	2 rises	9 yr	90 %	87 %	80 %	67 %
Critz (1998)[23]	689	I-125+EBRT	T1-2	≧0.5	5 yr	94 %	93 %	74 %	69 %
Dattoli (2003)[24]	102	Pd-103+EBRT	T2a-T3	≧1.0	4 yr	82 %		85 %	75 %
Grado (1998)[25]	490	I-125/ Pd-103±EBRT	T1-3	2 rises	5 yr	88 %		72 %	57 %
Grimm (2001)[26]	125	I-125	T1-2b	2 rises	10 yr	97 %	78 %	86 %	55 %
Ragde (2000)[27]	147	I-125/ Pd-103	T1-3	3 rises	12 yr	66 %			
	82	I-125/ Pd-103+EBRT		3 rises	12 yr	79 %			
Stock (1997)[28]	258	I-125/ Pd-103	T1-2	2 rises	4 yr	75 %		74 %	34 %
Sharkey (2000)[29]	65	Pd-103		≧1.5	4 yr	90 %	75 %	57 %	—
Zelefsky (2000)[30]	248	I-125	T1c-2b	3 rises	5 yr	96 %	84 %	62 %	

Association of Physics and Medicine (AAPM) のTask Group No. 43 (TG-43) により線量計算アルゴリズムの変更が勧告されており[33]，^{125}Iシードによる前立腺永久挿入密封小線源治療に関するABSによる処方線量のガイドラインも単独治療で160Gyより144Gyへ変更された。40-50Gyの外照射を併用する場合は110～120Gyより100～110Gyへ変更されている。挿入後の線量評価の実施も勧告されているが最適な時期は明らかでなく，挿入後4週間頃のCT実施が報告されている。記載すべき線量としては①処方線量，②前立腺体積を100%含む線量であるD_{100}，③前立腺体積を90%含む線量であるD_{90}，④処方線量を照射される前立腺体積の比率V_{100}が勧告されている。

高線量率^{192}Ir線源による高線量率組織内照射は，本邦では永久挿入密封小線源が使用できなかった為，前立腺がんに応用されてきた。従来の報告の多数は欧米での放射線物理学的・生物学的利点を利用した検討であり，ほとんどが外照射との併用である。

4．前立腺全摘術後のPSA再発

根治的前立腺全摘術後25-35%に再発を生じるとされ[34-35]，局所再発例には放射線治療，遠隔転移例には内分泌療法が施行されている。再発形式のひとつとして，術後の経過観察中に局所再発が画像上は明らかでないもののPSAの上昇を認めるPSA再発がある。表5に根治的前立腺全摘術後のPSA再発に対する放射線治療成績を示す。PSA倍加時間が短いほど，早期に臨床的再発が生じることが指摘されており[46]，局所再発か遠隔転移かを予測する因子としては，術後PSA再発までの期間が2年以内，PSA倍加時間が6ヵ月未満，Gleason scoreが8以上のものが遠隔転移と相関する因子とする報告がある[47]。根治的前立腺全摘術後のPSA再発に対する標準的治療法は確立されていないが，1997年ASTRO (American Society for Therapeutic Radiology and Oncology) Consensus Panelにおいて根治的前立腺摘出後PSA上昇に対する放射線治療の解析がおこなわれ，1999年にConsensus Panel Statementとして報告された[48]。Massachusetts General Hospital (Zietman)・Washington University (Hudson)・Mayo Clinic (Schild)・Wayne State University (Forman) のデータの解析より総線量64Gy以上で通常分割照射（1回線量1.8～2.0Gy）が推奨された。治療のタイミングについては，Parkerらの分析より早期の放射線治療の有効性が示されつつある[49]。

おわりに

前立腺がんの放射線治療の選択肢は，外照射や永久挿入密封小線源治療および粒子線治療な

表5　根治的前立腺全摘術後のPSA failureに対する放射線治療

Author	No.	Median pre-RT PSA	Gleason score 8-10	Seminal Vesicle+ or LN+	Dose Median	Follow-up Median	Biochemical Control
Leventis[45]	49	2.1	7%	27%	66Gy	29 mos	24%/5-yr
Catton[46]	43		15%	35%	60Gy	43 mos	20%/5-yr
Pisansky[47]	166	0.9	16%	31%	64Gy	52 mos	46%/ 5-yr
Anscher[48]	89	1.4	26%	34%	66Gy	48 mos	50%/ 4-yr
Nudell[49]	69	0.1-29.3	22%	10%	60-74Gy	37 mos	47%/4-yr
Cadeddu[50]	82	2.8(mean)	15%	15%	64Gy (mean)	8.3 years (mean)	10%/ 5-yr
Garg[51]	78	1.2	35%	38%	66Gy	25 mos	57/78
Do[52]	60		17%	37%	64.8Gy	36 mos (mean)	30/60
Morris[53]	48	1.7	34%	25%	60-64Gy	32 mos (mean)	47%/3-yr
Crane[54]	41	2.7	35%	29%	60Gy	55 mos	8/41

ど多岐にわたり，その最適な選択については今後の検討課題となっている。外照射は3D-CRTやIMRTの応用により，永久挿入密封小線源治療および粒子線治療はその物理学および生物学的特性により，正常組織の線量軽減による有害事象の制御と総線量の増加による治療効果の向上を目指している。治療の選択にあたっては，臨床病期や治療前PSA，Gleason Scoreおよび前立腺の容積や形態，合併症の有無などの総合的な検討が必要である。

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Pro-Gastrin–Releasing Peptide as a Factor Predicting the Incidence of Brain Metastasis in Patients with Small Cell Lung Carcinoma with Limited Disease Receiving Prophylactic Cranial Irradiation

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BACKGROUND. Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis with an effect on overall survival in patients with small cell lung carcinoma (SCLC). In spite of multidisciplinary intensive treatment approaches, many patients still experience brain metastasis. The authors retrospectively analyzed the characteristics of the first failure event due to brain metastasis (FBM) in patients treated with PCI.

METHODS. Between January 1990 and April 2004, 71 patients with limited disease SCLC were treated with PCI after completing systemic treatment at the National Cancer Center Hospital (Tokyo, Japan). Univariate and multivariate analyses were used to identify factors related to FBM and survival.

RESULTS. The FBM and overall incidence of brain metastasis (OBM) were 16.9 % (12 of 71) and 26.8% (19 of 71), respectively. Median time to progressive disease and median survival were 8.4 months and 21.6 months, respectively. Elevation of pro-gastrin–releasing peptide (Pro GRP) level before PCI was found to be a significant predictive and prognostic factor for FBM, OBM, and survival on multivariate analysis ($P = 0.007$, $P = 0.025$, and $P = 0.009$, respectively).

CONCLUSIONS. An elevated Pro GRP level before PCI was found to be significantly related to FBM and survival, and should be considered before PCI is performed. *Cancer* **2005;104:811–6.** © *2005 American Cancer Society.*

KEYWORDS: prophylactic cranial irradiation, small cell lung carcinoma, limited disease, predictive factor, pro-gastrin–releasing peptide.

Small cell lung carcinoma (SCLC) accounts for approximately 20% of all lung carcinomas.[1] Although SCLC rapidly develops distant metastasis, it is very sensitive to chemoradiotherapy, unlike non-SCLC. Limited disease SCLC is clinically confined to the hemithorax, and chemoradiotherapy is the standard treatment. In patients with limited disease SCLC, chemotherapy combined with thoracic radiotherapy yields complete remission (CR) rates of 50–85%, with a median survival time of 12–20 months.[2–4] The 5-year survival rate is reported to be 26% for patients who have CR.[4] Because chemoradiotherapy reduces the risk of intrathoracic disease recurrence, distant metastasis in the brain has been the main cause of disease recurrence. Although only 10% of patients have brain metastasis at the time of diagnosis, the cumulative incidence at 2 years is > 50%.[5,6] As many as 73% of patients develop clinically apparent central nervous system metastases before death,[7,8] and even higher rates are documented in autopsy series.[9] The brain is the initial site of disease recurrence in 5–

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Received November 1, 2004; revision received March 7, 2005; accepted March 22, 2005.

DOI 10.1002/cncr.21238
Published online 22 June 2005 in Wiley InterScience (www.interscience.wiley.com).

33% of patients, and is the only site of disease recurrence in ≤ 20% of patients.[10,11]

Although several randomized trials of prophylactic cranial irradiation (PCI) have attempted to reduce the risk of brain metastasis and to improve survival, to our knowledge its role in the management of patients with SCLC has remained controversial according to the results of each trial.[12–14]

Recently, the metaanalysis of these trials comparing PCI with no-PCI found that PCI led to a small but significant absolute reduction in mortality (5.4%), and that PCI not only significantly reduced the risk of brain metastasis, but also improved both overall survival (OS) and disease-free survival among patients with SCLC in CR.[15] These results suggest that PCI should be considered as a part of the standard treatment for patients with limited disease SCLC who achieved CR or good partial remission (PR).

Although PCI was performed for patients who achieved CR or good PR as part of the combined treatment that consisted of chemotherapy and thoracic radiotherapy, brain metastasis occurred in 4–24% of the treated patients.[6,12–14] Whole-brain irradiation (WBRT) for brain recurrence was often difficult because these patients had already received PCI to the whole brain. Therefore, we should strictly consider PCI for patients who could achieve a true CR, as assessed with diagnostic imaging. In addition, we should be careful to follow the patients who have a high risk of brain recurrence after PCI.

To our knowledge, there are no previous reports that describe the characteristics of patients with brain metastasis after PCI. In the current study, we analyzed retrospectively predictive factors for brain metastasis in patients with limited disease SCLC treated with PCI.

MATERIALS AND METHODS

Patients

A total of 71 patients with limited disease SCLC were treated with PCI after chemoradiotherapy for primary disease between January 1990 and April 2004 at the National Cancer Center Hospital (Tokyo, Japan). Fifty-four patients were male, and the median age was 62 years old (range, 40–75 years).

Histologic or cytologic examination confirmed the diagnosis of SCLC in all patients. Before the initiation of systemic treatment, staging was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and brain, as well as radionuclide bone scanning and bone marrow aspiration and biopsy. Limited disease was defined as being limited to one hemithorax, mediastinal, hilar, or supraclavicular area, which could be encompassed within a reasonable single radiation portal. Patients with pleural effusion found on chest films or CT scan were excluded.

Tumor response was classified in accordance with the World Health Organization (WHO) criteria.[16] After systemic treatment, including thoracic radiotherapy, PCI was administered to patients with CR or good PR according to the results of chest radiography and CT or MRI scans of the head, chest, and abdomen.

Thoracic Radiotherapy

The majority of patients (n = 55 [77.5%]) received accelerated twice-daily thoracic radiotherapy comprised of 45 gray (Gy) in 1.5-Gy fractions. The remaining patients (n = 16 [22.5%]) received once-daily radiotherapy, 50 Gy in 2-Gy fractions. Radiotherapy was performed 5 days per week, excluding weekends and holidays. Sixty of the 71 patients received concurrent chemoradiotherapy, which began on Day 2 of the first cycle of combination chemotherapy as cisplatin (80 mg/m^2, Day 1) plus etoposide (100 mg/m^2, Days 1, 2, and 3). The other patients received sequential thoracic radiotherapy after the forth cycle of chemotherapy.

The initial field included the primary tumor volume with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was tumor involvement).

Chemotherapy

All patients received cisplatin combination chemotherapy. After concurrent chemoradiotherapy, 34 patients received 3 cycles of cisplatin plus etoposide, 17 patients received CODE therapy (cisplatin at a dose of 25 mg/m^2 weekly for 6 weeks; vincristine at a dose of 1 mg/m^2 during Weeks 2, 4, and 6; and doxorubicin at a dose of 40 mg/m^2 and etoposide at a dose of 80 mg/m^2 for 3 days during Weeks 1, 3, and 5), and 9 patients received 3 cycles of cisplatin (60 mg/m^2, Day 1) plus irinotecan (60 mg/m^2, Days 1, 8, 15). In patients treated with sequential radiotherapy, five patients received four cycles of cisplatin plus etoposide, four patients received four cycles of cisplatin plus irinotecan, and two patients received four cycles of cisplatin containing combination chemotherapy, optimized for each patient.

Prophylactic Cranial Irradiation

All patients who achieved CR (n =40 [56.3%]) or good PR (n = 31 [43.7%]) were treated with PCI. The median time between the initiation of systemic induction treatment and the initiation of PCI (duration) was 3.7 months (range, 2.6–7.5 months).

The target volume was the entire intracranial site. Individual shaped ports with multileaf collimators

were used to define the irradiation target volume. Patients were treated using a megavoltage linear accelerator with 4–6 megavolt (MV) photons. Treatment was delivered with equally weighted right and left lateral fields, with the dose calculated on the central ray at mid-separation of the beams.

Of the 71 patients who received PCI, the majority of patients (52 of 71 [73.2%]) received 25 Gy in 2.5-Gy fractions daily, 12 patients received 30 Gy in 2-Gy fractions daily, 6 patients received 24 Gy in 1.5-Gy fractions twice daily, and 1 patient received 36 Gy in 2-Gy fractions daily. All PCI was performed a total of 5 days per week. The treatment was administered with a linear accelerator of 6 MV (n = 53 patients) or 4 MV (n = 18 patients). The median follow-up time after PCI was 16.3 months (range, 1.4–113.6 months).

Statistical Analysis

The first failure event due to brain metastasis (FBM) was defined as brain metastasis as a first event after PCI, and the overall incidence of brain metastasis (OBM) was defined as the overall incidence of brain metastasis found throughout the clinical course after PCI. Clinical and laboratory variables before PCI were chosen by considering possible factors indicated by our own experience. We determined the predictive factors for FBM and OBM using both univariate (Pearson chi-square test/Fisher exact test) and multivariate analysis.

Before PCI, 9 categorized variables for multivariate analysis were selected, as follows: gender (male vs. female), age (< 60 vs. ≥ 60 years), response to systemic treatment (CR vs. good PR), time between the start of systemic treatment and the start of PCI (duration: < 4 months vs. ≥ 4 months), hemoglobin level (< 10 g/dL vs. ≥ 10 g/dL), lactate dehydrogenase level (≤ 229 U/L vs. > 229 U/L), C-reactive protein (≤ 0.1 mg/dL vs. > 0.1 mg/dL), neuron-specific enolase (NSE) (≤ 10 ng/mL vs. > 10 ng/mL), and pro-gastrin–releasing peptide (Pro GRP) (≤ 46 pg/mL vs. > 46 pg/mL).

Time to progressive disease (PD) was measured from the first day of PCI until PD or the last day of follow-up without PD, and OS time was measured from the first day of PCI until death or the last day of follow-up. Median time to PD and median OS were estimated using the Kaplan–Meier method. Prognostic factors were evaluated by multivariate analysis. All statistical analyses were performed using SPSS version 12.0J (SPSS Inc., Chicago, IL).

RESULTS

Incidence of Brain Metastasis

FBM and OBM were observed in 16.9% (12 of 71; 95% confidence interval [95% CI], 8.2–17.3%) and 26.8% (19 of 71; 95% CI, 16.5–27.3%) of patients, respectively. Nine patients with FBM had multiple brain metastases and the others had solitary lesions. Among these patients, six were reirradiated with WBRT or stereotactic multiarc radiotherapy, five were treated with systemic chemotherapy, and one received best supportive care. The median times to FBM and OBM were 9.4 months (range, 1.1–23.5 months) and 12.0 months (range, 1.1–92.9 months), respectively. In univariate analysis, an elevated Pro GRP level was found to be significantly related to FBM and OBM (Table 1) (P = 0.007 and P = 0.029, respectively). Using a complete dataset from

TABLE 1
Univariate Analyses of Pretreatment Variables for FBM and OBM

Variables	No. of patients	No. of FBM	P value	No. of OBM	P value
Gender			0.27		0.99
Male	54	11		15	
Female	17	1		4	
Age (yrs)			0.71		
≥ 60	38	7		11	0.66
< 60	33	5		8	
Energy (MV)			0.99		0.36
4	18	3		3	
6	53	9		16	
Total dose (Gy)			0.99		0.08
≤ 25	58	10		13	
> 25	13	2		6	
Hyperfraction			0.27		0.33
Twice daily	6	2		3	
Once daily	65	10		16	
Response			0.63		0.70
Good PR	31	6		9	
CR	40	6		10	
Duration (mos)[a]			0.61		0.86
≥ 4	25	5		7	
< 4	46	7		12	
Hemoglobin level (g/dL)			0.75		0.79
< 10	43	8		12	
≥ 10	28	4		7	
LDH level (U/L)			0.99		0.99
> 229	6	1		1	
≤ 229	65	11		18	
CRP level			0.75		0.50
> 0.1 mg/mL	42	8		10	
≤ 0.1 mg/dL	29	4		9	
NSE level (ng/mL)			0.63		0.99
> 10	8	2		2	
≤ 10	59	10		16	
Pro GRP level (pg/mL)			0.007		0.029
> 46	12	5		5	
≤ 46	37	2		4	

FBM: first failure event due to brain metastasis, OBM: overall incidence of brain metastasis, MV: megavolt; Gy: grays; PR: partial remission, CR: complete remission; LDH: lactate dehydrogenase, CRP: C-reactive protein; NSE: neuron- specific enolase; Pro GRP: pro-gastrin-releasing peptide.
[a] Duration indicates the time between the initiation of systemic induction treatment and the initiation of prophylactic cranial irradiation.

TABLE 2
First Progressive Disease Sites after PCI

Site	No. of patients	% of all patients
Local failure (inside the thorax)	20	28.2
Distant metastasis[a]	26	36.6
Abdominal organ	7	9.9
Bone	9	12.7
Spinal cord	1	1.4
Brain	12	16.9
Total	46	64.8

PCI: prophylactic cranial irradiation.
[a] Three patients had more than one progressive disease site in distant metastasis.

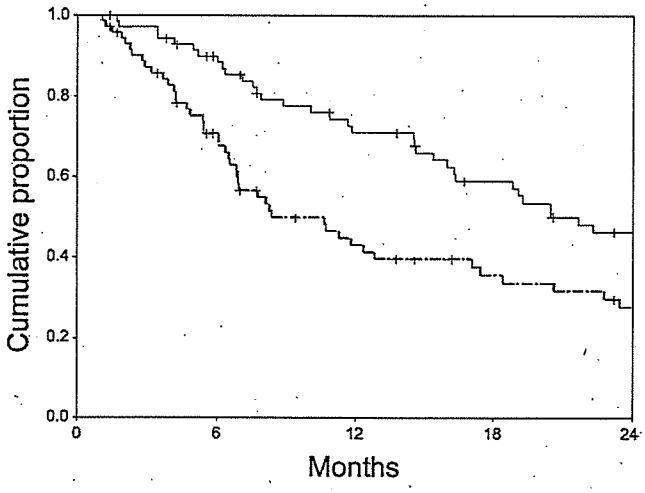

FIGURE 1. Kaplan–Meier analysis of time to disease progression (dotted line) and overall survival (solid line).

49 patients, a multivariate logistic regression model disclosed that an elevated Pro GRP level was a significant predictive factor for both FBM (hazard ratio [HR], 12.5; 95% CI, 2.00–77.9 [$P = 0.007$]) and OBM (HR, 5.89; 95% CI, 1.25–27.7 [$P = 0.025$]).

Time to Progressive Disease and Survival

In the current series, the majority of patients (46 of 71 [64.8%]; 95% CI, 53.7–65.4%) experienced PD in their clinical courses. The first sites of PD are listed in Table 2. The median time to PD and the median survival time were 8.4 months (95% CI, 3.9–12.8 months) (Fig. 1)and 21.6 months (95% CI, 14.1–29.2 months) (Fig. 1), respectively. A multivariate Cox regression model indicated that elevated Pro GRP level before PCI was a prognostic factor (HR, 2.97; 95% CI, 1.31–6.75 [$P = 0.009$]).

DISCUSSION

It is suggested that PCI eradicates subclinical brain metastasis that is protected from cytotoxic drugs by the blood-brain barrier as a pharmacologic sanctuary.[17] A recently reported metaanalysis of seven prospectively randomized trials demonstrated both an OS and disease-free survival advantage for patients with limited disease SCLC who received PCI compared with patients who did not receive PCI.[15] However, the metaanalysis included various trials and often insufficient systemic chemotherapy regimens, different PCI techniques, and a mixed population of patients with limited and extensive disease.[12–15] Therefore, Kotalik et al.[18] found there was insufficient evidence to make a definitive recommendation in terms of the total dose, fractionation, indication, and timing of PCI according to this metaanalysis.

In the current study, 16.9% of patients had brain metastasis as a first site of failure, which is consistent with previous reports of 4–24%.[6,12–14] The salvage treatment for brain metastasis after PCI would be restricted by the number of brain metastases, patient condition, and previous irradiation. To our knowledge, no report has described the predictive or prognostic factors for outcomes after PCI. Therefore, our results could provide useful information concerning the indication of PCI and close follow-up in patients with limited disease SCLC with CR or good PR who received intensive multidisciplinary treatment.

We found that elevated Pro GRP level before PCI was a significant predictive factor for FBM and for OBM ($P = 0.007$ and $P = 0.025$, respectively). The other pretreatment variables such as clinical and laboratory parameters had no influence on FBM or OBM. Among tumor markers, NSE is known to have a high false-positive rate due to hemolysis, whereas Pro GRP is a stable and reliable tumor marker for SCLC.[19] In addition Pro GRP is found to have higher specificity than NSE, and its serum level was frequently elevated at an earlier stage compared with that of the NSE level in patients with SCLC at the time of diagnosis.[20,21] It is reported that Pro GRP reflects tumor volume and the effect of treatment more sensitively than does NSE, and that it is useful in detecting PD because Pro GRP levels increase before disease recurrence becomes evident.[19,21,22] From the results of the current study, the elevation of Pro GRP before PCI might reflect the existence of residual viable tumor cells after a series of induction treatments, even if CR or good PR is indicated by imaging. A PCI would be recommended for patients with limited and extensive disease SCLC with CR.[15] However, PCI might not be sufficiently beneficial for decreasing the incidence of brain metastasis in patients with an elevated Pro GRP level. Therefore, by the completion of whole therapy, we should completely eliminate residual subclinical intracranial

and/or extracranial disease that causes the brain recurrence.

Several evidence-based guidelines for limited disease SCLC described uncertainty in terms of the optimal regimen, schedule of drug administration, duration of chemotherapy, and maintenance chemotherapy.[23,24] Although there is a guideline that recommends a maximum of six cycles of chemotherapy,[23] the trend in clinical trials and practice, including the current study, has been to use only four cycles of cisplatin-based chemotherapy. In patients with CR with elevated Pro GRP after four cycles of chemotherapy, two additional cycles of chemotherapy might be possible to eliminate tumor cells, to normalize Pro GRP levels, and to reduce the risk of brain recurrence.

A previous study suggested that there may be a dose-response relation for PCI, and that higher doses were more effective in reducing the risk of brain metastasis.[14] If currently ongoing trials that compare 25 Gy in 10 fractions with 36 Gy in 18 fractions[18] indicate the superiority of high-dose PCI, this will be another option to optimize the PCI procedure for controlling the subclinical disease at pharmacologic sanctuary.

The previous WHO criteria for evaluation of tumor response[11] did not consider the value of tumor markers. However, the Response Evaluation Criteria in Solid Tumors (RECIST) include tumor markers for assessment of CR.[25] Serum laboratory methods more accurately evaluate the evidence of viable tumor cells, and have a complementary role to the imaging studies when macroscopic tumor disappears or residual scar remains. In SCLC, tumor markers are well correlated to the response and tumor volume,[19,21,22] as was observed with Pro GRP in the current study. Therefore, CR according to the RECIST guidelines might be more appropriate in the evaluation of patients with SCLC for PCI.

Several authors reported many prognostic factors of clinical and laboratory parameters for patients with SCLC.[26] Almost all the analyses in the previous reports showed pretreatment factors before the initiation of systemic therapies. We analyzed pretreatment parameters for patients with CR or good PR receiving PCI. In our study, most of the laboratory parameters fell within normal limits before PCI, except for Pro GRP as a prognostic factor.

Local failure occurred in approximately one-half of the patients with disease recurrence, in addition to distant failure. The Southwest Oncology Group reported the pattern of failure in 114 patients with limited disease SCLC treated with cisplatin plus etoposide and concomitant thoracic radiotherapy followed by PCI. Local failure and distant metastasis occurred in 49% and 35% of patients, respectively.[27] These results also suggested that the main cause for disease recurrence was local or distant failure. Therefore, it is crucial to develop new drugs or regimens for improving local and distant control, which achieve a high rate of CR without elevation of tumor markers such as Pro GRP before PCI.

The results of the current study demonstrate that elevation of Pro GRP before PCI is a significant predictive factor for the first failure event due to brain metastasis. With regard to the indication of PCI, the assessment of clinical response according to RECIST might be evaluated more accurately using Pro GRP together with conventional imaging studies.

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Bone Marrow Transplantation (2005) 35, 763–766

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A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement

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Summary:

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation. Since retinoblastoma is highly chemosensitive, dose-escalation of chemotherapeutic agents with stem cell support should be promising. We report our experience with high-dose chemotherapy (HDC) and autologous stem cell transplantation (SCT) in patients with metastatic retinoblastoma. Five patients with metastatic retinoblastoma underwent HDC with autologous SCT following conventional chemotherapy and local radiation therapy. Stem cells (bone marrow in four and peripheral blood stem cells in one) were collected after marrow involvement was cleared. Melphalan was a key drug in all patients, and was administered in combination with other agents such as cisplatin, cyclophosphamide, carboplatin or thiotepa. Three patients are currently alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT. They had no central nervous system (CNS) involvement. The two patients who died of disease had CNS involvement. No long-term sequelae of HDC have been noted. Our treatment strategy using HDC appears to be effective for treating metastatic retinoblastoma without CNS involvement.

Bone Marrow Transplantation (2005) **35**, 763–766.
doi:10.1038/sj.bmt.1704882
Published online 7 March 2005
Keywords: retinoblastoma; metastasis; high-dose chemotherapy; autologous stem cell transplantation; melphalan

Retinoblastoma, the most common ocular malignancy in childhood, develops in infants, and the incidence is one in 160 000–20 000 births in Japan.[1] Many therapeutic modalities have been employed, and retinoblastoma has become one of the curable pediatric solid tumors. Nevertheless, the prognosis of extraocular retinoblastoma with metastasis to bone/bone marrow (BM) or the central nervous system (CNS) remains very poor.[2] Such high-risk populations include involvement of the cut end of the optic nerve, extrascleral spread into the orbit, lymphatic or hematogenous dissemination, CNS involvement and trilateral retinoblastoma. The overall occurrence of extraocular retinoblastoma was 4.8% of all patients at an institution.[3] Since retinoblastoma is highly chemosensitive, a treatment strategy that includes the dose-escalation of chemotherapeutic agents and stem cell support should be promising. We treated five patients with metastatic retinoblastoma using high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (SCT), and three patients are currently alive and disease-free. Although our experience is very limited, our experience suggests the feasibility of a prospective study.

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Received 4 February 2004; accepted 15 December 2004
Published online 7 March 2005

Patients and methods

Five patients received HDC for extraocular retinoblastoma between March 1986 and November 2000 at the National Cancer Center Hospital of Japan (NCCH), and the data reported reflect the last patient contact as of January 2004. All patients originally were treated with radiation therapy and/or enucleation for intraocular disease at NCCH. The clinical characteristics of the patients are described in Table 1. After completion of the initial series of local ophthalmic therapies in NCCH, four of the five patients developed metastatic recurrence, as reported elsewhere.[4–6] Only one patient had BM metastasis at the initial diagnosis. Staging studies included computed tomography and magnetic resonance imaging of orbits and brain, histopathologic evaluation of BM aspiration and cytologic examination of cerebrospinal fluid (CSF). All patients were classified as having stage III/IV disease by the grading system of Grabowski and Abramson.[7] After the diagnosis of metastatic diseases was established, all patients were treated with conventional chemotherapy with or without radiotherapy and surgical enucleation (Table 2). Systemic chemotherapy included courses of vincristine, cyclophosphamide and doxorubicin with or without cisplatin alternating with cisplatin and cyclophosphamide, or

Table 1 Patients characteristics

UPN	Sex	Age at diagnosis	Involvement	Metastases at diagnosis	Treatment	Metastases after therapy
1	F	3 months	Bilateral	None	Right: 50.7 Gy radiation Left: enucleation	Brain (optic chiasm), spinal cord (L1)
2	M	10 months	Bilateral	None	Right: 49.4 Gy radiation Left: enucleation	Brain (ethmoid and sphenoid sinus), bilateral cervical LNs
3	F	41 months	Left	None	Left: 46 Gy radiation + HIT	Right temporal bone, marrow (70%)
4	F	16 months	Right	Marrow	Right: enucleation + 6 Gy radiation + chemotherapy	
5	F	18 months	Right	None	Right: 46 Gy radiation + enucleation + HIT + PC + CTT + IVI	Right orbit, marrow (50%)

UPN = unique patient number; HIT = heat-inducing thermotherapy; PC = photocoagulation; CTT = chemothermotherapy; IVI = intravitreal injection.

Table 2 Therapy and outcome

UPN	Cx. after Mets	Rx. after Mets	SCT from relapse (mos)	Conditioning (mg/m^2)	Stem cell source	Result	Meta. after SCT (mos)	Sequelae
1	VCR/CY/ADR ×2 CY/CDDP ×1	Spine 40 Gy, cranium 25 Gy + boost 15 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Spinal cord at Th12-L1 level (24 mos)	NE
2	VCR/CY/ADR ×3 CDDP/ETO ×2	Cranium 40 Gy + boost 20 Gy, spine 21 Gy, cervical LNs 40 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Rt. cervical LN (4 mos)	NE
3	VCR/CY/ADR ×4 CDDP/ETO ×2	Focal site 40 Gy	7	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (113+)	None	None
4	VCR/CY/ADR ×3 CDDP/ETO ×3	—	6	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (107+)	None	None
5	VCR/CY/ADR/ CDDP ×3 CBP/ ETO ×4	—	7	L-PAM 160, CY 120 mg/kg, TEPA 500	PBSC	NED (38+)	None	None

SCT = stem cell transplantation; BM = bone marrow; CNS = central nervous system; LN = lymph node; NED = no evidence of disease; DOD = dead of disease; NE = not evaluable; VCR/CY/ADR = vincristine 1.5 mg/m^2/day × 1, cyclophosphamide 600 or 800 mg/m^2/day × 2, doxorubicin 40 mg/m^2/day × 1; CDDP/CY = cisplatin 90 mg/m^2/day × 1, cyclophosphamide 1200 mg/m^2/day × 1; CDDP/ETO = cisplatin 20 mg/m^2/day × 5, etoposide 100 mg/m^2/day × 5; VCR/CY/ADR/CDDP = vincristine 1.5 mg/m^2/day × 1, cyclophosphamide 1200 mg/m^2/day × 1, doxorubicin 40 mg/m^2/day × 1, cisplatin 18 mg/m^2/day × 5; CBP/ETO = carboplatin 120 mg/m^2/day × 5, etoposide 100 mg/m^2/day × 5; L-PAM = melphalan; VP-16 = etoposide; CBDCA = carboplatin; TEPA = thiotepa.

cisplatin and etoposide, or carboplatin and etoposide. After complete response of tumor involvement in the BM, autologous BM cells were collected from four patients, autologous blood stem cells from one patient, respectively. The nonpurged stem cells were cryopreserved. All patients also received one to five intrathecal injections of methotrexate at a variable dose of 5–12.5 mg/dose, concomitant with systemic chemotherapy. Radiation therapy was given in four patients to sites that had harbored bulky disease at early stage after the diagnosis of metastasis. All patients were prepared for HDC with SCT after achieving complete remission, which was evaluated by imaging studies, BM aspiration and/or CSF examination. We harvested BM cells or peripheral blood stem cells, if a BM aspirate had no tumor cells on morphologic analysis before harvesting. We did not apply minimum residual disease (MRD) studies on BM cells or peripheral blood stem cells. Conditioning regimens for all patients contained melphalan 180 mg/m^2 as a key drug. Concomitant agents were cisplatin 90 mg/m^2 and cyclophosphamide 120 mg/kg (case 1, 2), etoposide 800 mg/m^2 and carboplatin 1600 mg/m^2 (case 3, 4), or thiotepa 500 mg/m^2 and cyclophosphamide 120 mg/kg (case 5). The collected BM cells ($1.0–1.7 \times 10^8$ total nucleated cells/kg) or peripheral blood stem cells (4.7×10^6 CD34+ cells/kg), which were unmanipulated, were infused approximately 24 h after completion of the conditioning chemotherapy. Granulocyte-colony stimulating factor was administrated intravenously once daily from day +5 or +7, and was continued until engraftment of neutrophils was established (case 3–5).

Results

Engraftment

Engraftment of neutrophils, defined as the first of two consecutive days of an absolute neutrophil count of at least 0.5×10^9/l, occurred 18, 26, 10, 14 and 11 days, respectively, after stem cell rescue. Platelet engraftment, defined as the first of 2 consecutive days of an absolute platelet count of at least 50×10^9/l sustained without transfusion, occurred 67, 32, 11, 51 and 16 days, respectively, after stem cell rescue.

Toxicities

All patients developed severe mucositis with oropharyngeal pain (WHO grade 3) after SCT. Only one patient had elevated transaminase levels greater than five times normal (case 5). All patients developed febrile neutropenia without a detectable pathogen, which subsided within 7 days by antibiotic treatment. No other acute toxicities associated with SCT were observed.

Patient survival

All three patients without CNS metastasis are alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT (case 3–5). They are alive without complications, except for orbital growth retardation because of local irradiation and surgical enucleation. Two patients died of recurrent diseases 4 and 48 months, respectively, after SCT (case 1, 2). There was no second malignancy in this series.

Discussion

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation therapy.[2,8] Honavar *et al*[9] have shown that postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting high-risk histopathologic characteristics.[9] Several centers have used conventional-dose chemotherapy and radiation therapy for hematogenously spread extraocular disease. Despite some reports of long-term event-free survival,[7,10] the bulk of the evidence suggests that the prognosis remains poor with such an approach.[11]

A limited number of studies and case reports have suggested that HDC with autologous stem cell rescue might be beneficial for patients with metastatic retinoblastoma (Table 3).[12–20] Namouni *et al*[14] conducted a study of HDC consisting of carboplatin, etoposide and cyclophosphamide (CARBOPEC) followed by autologous SCT in 25 patients, including 12 patients with distant metastases. Among eight children with bone and BM metastases, five survived between 11 and 70 months disease free, while three patients with CNS metastases relapsed in the CNS after HDC and died. Thus, the CARBOPEC regimen appeared to be effective only for patients with bone and/or BM involvement of retinoblastoma. Dunkel *et al*[16] reported four retinoblastoma patients with orbit and BM metastases who underwent HDC consisting of carboplatin and thiotepa with or without etoposide. All patients survived event-free for 46–80 months after the diagnosis of metastatic disease. They concluded that this treatment strategy is effective for metastatic retinoblastoma without CNS involvement. Rodriguez-Galindo *et al*[19] reported four retinoblastoma patients with bone and BM metastases, treated by intensive systemic therapy. Although they did not mention an effectiveness of HDC, they concluded that the use of intensive multimodal approach in patients with metastatic retinoblastoma without CNS involvement could achieve long-term survival.

The important component in HDC is the alkylating agents, which have favorable toxicity profile. There are some reports that thiotepa is effective for high-risk retinoblastoma and other malignancies.[16,19,21,22] As it penetrates well into the brain, as demonstrated by similar drug levels in CSF and in serum after intravenous injection bolus use, we should consider the high-dose thiotepa in the attempts of HDC in disseminated retinoblastoma, particularly with CNS involvement. However, we used not thiotepa but melphalan for HDC. High-dose melphalan and SCT have been used to treat neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma in children.[23–26] In addition, Inomata and Kaneko[27] suggested that retinoblastoma was most sensitive to melphalan based on a colony assay on double agar layers. Kaneko treated six patients with intraocular retinoblastoma that recurred after irradiation therapy by injecting 40 mg/m^2 of melphalan into the ipsilateral intracarotid artery, and by applying ocular hyperthermia (45°C, 1 h).[5] Two patients were cured (no recurrence for more than 10 years) with a single treatment procedure while preserving adequate visual function. Based on their observation, we selected melphalan as a key drug for HDC. We should consider that not only thiotepa but also melphalan is an effective agent of HDC for retinoblastoma. As other agents, busulfan and nitrosurea drugs

Table 3 High-dose chemotherapy for retinoblastoma

Author (year)	*n*	*Marrow involvement (+/−)*	*Bone Metastasis (+/−)*	*CNS Metastatsis (+/−)*	*High-dose chemotherapy*	*Result*
Namouni *et al* (1997)[14]	12	1/11	7/5	4/8	CARBOPEC	6 alive
Dunkel *et al* (2000)[16]	4	3/1	4/0	0/4	CTE 3, TC 1	4 alive
Kremens *et al* (2003)[19]	5	4/1	2/3	0/5	CTE 4, BCyE 1	5 alive[a]
Rodriguez-Galindo *et al* (2003)[20]	4	4/0	4/0	0/4	CE 1, BuCyM 1, CyE 1, CyTopo 1	2 alive
Jubran *et al* (2004)[3]	4	1/3	2/0	1[b]/3	CTE	2 alive
Our cases	5	2/3	2/3	2/3	CDDP-CyM 2, MEC 2, TCyM 1	3 alive

[a]One alive after relapse.
[b]Pineal.
CARBOPEC = carboplatin + etoposide + cyclophosphamide; CTE = carboplatine + thiotepa + etoposide; TC = thiotepa + carboplatin; BcyE = busulfan + cyclophosphamide + etoposide; CE = carboplatin + etoposide; BuCyM = busulfan + cyclophosphamide + melphalan; CyE = cyclophosphamide + etoposide; CyTopo = cyclophosphamide + topotecan; CDDP-CyM = cisplatin + cyclophosphamide + melphalan; MEC = melphalan + etoposide + carboplatin; TCyM = thiotepa + cyclophosphamide + melphalan; DOD = dead of disease.

(nimustine, ranimustine), which are effective because of their capacity to cross the blood–brain barrier, have been used for retinoblastoma.[28,29]

We conclude that our treatment strategy that includes high-dose melphalan with autologous SCT and local irradiation is effective in patients with metastatic retinoblastoma without involvement of the CNS, although a wide variation in the HDC regimen made it difficult to judge the objective safety and efficacy of autologous SCT. A safer and more effective modality is required to better control CNS involvement. The possible risk of late sequelae secondary to additive toxicity by HDC and cranial radiation should be critically evaluated. Since metastatic retinoblastoma is a rare disease, a larger cooperative study is needed to clarify the safety and efficacy of this HDC strategy.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare.

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Radiotherapy and Oncology 80 (2006) 93–97
www.thegreenjournal.com

Treatment of lung damage

Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients

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Abstract

***Purpose*:** To disclose characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy.

***Methods and materials*:** Radiographic changes, symptoms, history of corticosteroid prescription, and clinical course after 50–70 Gy of thoracic radiotherapy were retrospectively evaluated in 385 lung cancer patients.

***Results*:** Radiation-induced lung injury was stable without corticosteroid in 307 patients (Group 1), stable with corticosteroid in 64 patients (Group 2), and progressive to death despite corticosteroid in 14 patients (Group 3). Fever and dyspnea were noted in 11%, 50% and 86% ($p < 0.001$), and in 13%, 44% and 57% ($p < 0.001$) patients in Groups 1–3, respectively. Median weeks between the end of radiotherapy and the first radiographic change were 9.9, 6.7 and 2.4 for Groups 1–3, respectively ($p < 0.001$). The initial prednisolone equivalent dose was 30–40 mg daily in 52 (67%) patients. A total of 16 (4.2%) patients died of radiation pneumonitis or steroid complication with a median survival of 45 (range, 8–107) days.

***Conclusion*:** Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily was selected for the treatment in many patients.

Keywords: Radiation pneumonitis; Radiotherapy; Lung cancer; Corticosteroid

Thoracic radiotherapy is widely used for the curative and palliative treatment of lung cancer. Radiation-induced lung injury was first described as early as 1922 [1,2], and two types of lung injury, radiation pneumonitis and radiation fibrosis, were recognized in 1925 [3]. Radiation pneumonitis occurs in 5–15% of patients who have received radiation therapy for lung cancer. Its clinical symptoms are characterized by cough, dyspnea and fever developing between 1 and 3 months after the end of radiotherapy. Distinctive radiographic changes of radiation pneumonitis are a ground-glass opacification or diffuse haziness in early phase, and then alveolar infiltrates or dense consolidation in late phase in the region corresponding to the irradiated area [4–7]. Radiation pneumonitis may persist for a month or more and subside gradually. In severe cases, however, pneumonitis progresses to death due to respiratory failure within few weeks [4].

Use of adrenocorticotropic hormone (ACTH) and cortisone for radiation pneumonitis in a case was first reported in 1951 [8], and 9 cases of radiation pneumonitis treated with cortisone therapy in the literature were reviewed in 1968 [9]. Although no case series or clinical trials of corticosteroid therapy have been reported since that time, prednisolone has been given in patients with severe pneumonitis in clinical practice. The initial dose of prednisolone, approximately 30–100 mg daily, and very slow tapering schedule are in agreement among experts [4–6,10], because early withdrawal results in aggravation of pneumonitis [11–13]. There is no consensus, however, about criteria to define when steroids are required for radiation-induced lung injury. The objective of this study is to disclose general characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy, to obtain data on the initiation criteria, dose, and taper schedule of corticosteroid therapy for further prospective trials.

Patients and methods

Consecutive lung cancer patients treated with thoracic radiotherapy at a total dose of 50–70 Gy in National Cancer

0167-8140/$ - see front matter doi:10.1016/j.radonc.2006.06.007

Center Hospital between January 1998 and December 2003 were subjects of this study. We retrospectively reviewed all chest X-ray films taken during 6 month period from the end of thoracic radiation to identify the first radiographic change and its progress. History of corticosteroid prescription, symptoms at the time of and one-month period after the first radiographic change in a chest X-ray film, and clinical course of radiation-induced lung injury were obtained from medical charts. The diagnosis of radiation-induced lung injury was defined as radiographic changes including opacification, diffuse haziness, infiltrates or consolidation conforming to the outline of the sharply demarcated irradiated area in a chest X-ray film. During clinical course, scarring (fibrosis) was developed within the irradiated area leading to a reduction in lung volume. In contrast, pulmonary infection spreads through anatomical structure of the lung, and the boundary of infiltrates corresponds to anatomical boundary of the lung. For patients with fever, the radiographical response to antibiotics was also evaluated. Observed differences in the proportions of patients in various patient subgroups were evaluated using Chi-square test. Differences between continuous variables were compared using Mann–Whitney tests. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Of 544 lung cancer patients receiving thoracic radiotherapy at a total dose of 50–70 Gy, 111 patients were excluded from this study because they were not evaluable: loss of follow-up in 88 patients, early lung cancer progression in 18 patients, chemotherapy-induced neutropenic fever and pneumonia in three patients, death of bleeding from the esophageal stent in one patient, and no chest X-ray films available in one patient. In addition, 48 patients (11% of 433 evaluable patients) were also excluded because no radiation-induced lung injury was noted. Thus, the subject of this study was 385 patients.

Of the 385 patients, 78 (20%) received corticosteroid therapy for radiation-induced lung injury, and 307 did not. Radiation-induced lung injury was stable without corticosteroid in the 307 (80%) patients (Group 1), stable or in remission with corticosteroid in 64 (17%) patients (Group 2), and progressive to death despite corticosteroid in 14 (4%) patients (Group 3). No difference in sex, total dose, intent of radiotherapy, and combination chemotherapy was noted among three Groups, but median age of patients was higher in Group 3 (Table 1). Fever was developed in 50% of patients in Group 3 at the initial radiographic change, and in 86% of them during subsequent clinical course, while it was developed in only 11–12% of patients in Group 1 through their clinical course (Table 2). Dyspnea was developed in 57% of patients in Group 3 and in 44% of patients in Group 2 during clinical course, while it was developed in only 14% of patients in Group 1 (Table 2). A total of 88 patients developed fever at the initial change in chest X-ray and/or during subsequent clinical course. Of these, 43 patients received antibiotics, but no radiographical response was obtained in these patients. Five (2%) and seven (2%) patients in Group 1 developed bloody sputum and chest pain, respectively, but none in Group 2 or 3 developed these symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was 1.7 weeks for group 1, 1.3 weeks for group 2, and 0.9 weeks for group 3 ($P < 0.001$, Table 3). Interval between the end of radiotherapy and the first change in a chest X-ray was shorter in Group 3 than in Group 2 or Group 1 (Table 3). Of 57 patients in whom the first radiographic change was noted within three weeks, 9 (16%) died of pneumonitis, while radiation-induced lung injury that occurred 10 weeks or later after the end of radiation was easily managed with or without steroid therapy (Table 3). Oxygen content in the blood at the start of steroid therapy was examined in 70 patients of Groups 2 and 3. Oxygen content

Table 1
Patient demographics and radiotherapy performance

Characteristics	Total *N* (%)	Group 1 *N* (%)	Group 2 *N* (%)	Group 3 *N* (%)	*p*-value
Total	385 (100)	307 (80)	64 (17)	14 (4)	
Sex					
Male	300 (78)	240 (78)	47 (73)	13 (93)	0.28
Female	85 (22)	67 (22)	17 (27)	1 (7)	
Age median (range)	65 (28–87)	63 (28–87)	65 (37–83)	71 (65–84)	0.008
Total dose (Gy)					
Median (range)	60 (50–70)	60 (50–70)	60 (50–61)	60 (50–60)	0.50
Intent of radiotherapy					
Curative	298 (77)	232 (76)	52 (81)	14 (100)	0.074
Palliative	87 (23)	75 (24)	12 (19)	0 (0)	
Chemotherapy					
None	121 (31)	101 (33)	15 (23)	5 (36)	0.48
Sequential	121 (31)	93 (30)	25 (39)	3 (21)	
Concurrent	143 (37)	113 (37)	24 (38)	6 (43)	

Table 2
Symptoms through clinical courses

Symptom	At the initial change in chest X-ray				During subsequent clinical course			
	Group 1	Group 2	Group 3	p	Group 1[a]	Group 2[b]	Group3[b]	p
Cough	96 (31)	35 (56)	5 (36)	0.001	85 (28)	38 (59)	5 (36)	<0.001
Sputum	32 (10)	11 (18)	4 (29)	0.049	30 (10)	11 (17)	3 (21)	0.12
Hemosputum	5 (2)	0 (0)	0 (0)	0.53	4 (1)	0 (0)	0 (0)	0.60
Chest pain	7 (2)	0 (0)	0 (0)	0.40	2 (0.6)	0 (0)	0 (0)	0.78
Fever								
None	269 (88)	35 (56)	7 (50)	<0.001	272 (89)	32 (50)	2 (14)	<0.001
37.0–37.9 °C	18 (6)	11 (18)	2 (14)	24 (8)	16 (25)	5 (35)		
38 °C≤	13 (4)	14 (22)	5 (36)	8 (3)	13 (20)	7 (50)		
Not specified	7 (2)	3 (4)	0 (0)	3 (1)	3 (4)	0 (0)		
Dyspnea	43 (14)	14 (22)	6 (43)	0.007	40 (13)	28 (44)	8 (57)	<0.001
Fever or dyspnea	75 (24)	37 (58)	10 (71)	<0.001	65 (21)	49 (77)	14 (100)	<0.001
Any	150 (49)	51 (81)	13 (93)	<0.001	118 (38)	60 (94)	14 (100)	<0.001

[a] During one month period following the initial change in the chest X-ray.
[b] At the start of steroid therapy.

Table 3
The chest X-ray intervals and first radiographic change

Weeks	Group 1	Group 2	Group 3	p-value
The average interval of chest X-rays (weeks)[a]				
Median (range)	1.7 (0.7 to 6.0)	1.3 (0.5 to 4.4)	0.9 (0.5 to 3.8)	<0.001
Duration between the end of radiotherapy and the first radiographic change (weeks)				
Median (range)	9.9 (−2.9 to 45.1)	6.7 (0 to 24.9)	2.4 (0.4 to 10.1)	<0.001
<6	82 (27)	26 (41)	11 (79)	<0.001
6–11.9	116 (38)	29 (45)	3 (21)	
12–17.9	71 (23)	7 (11)	0 (0)	
18≤	38 (12)	2 (3)	0 (0)	

[a] Calculated as follows: the average interval of chest X-rays = (the first radiographic change − the start of radiotherapy)/the number of chest X-rays taken during this period/7).

was slightly decreased (PaO2 = 70–74.9 Torr) in 12 (19%) patients of Group 2 and one (7%) patient of Group 3, and moderately to severely decreased (PaO2 ≤ 69.9 Torr or SpO2 ≤ 92%) in 21 (33%) patients of Group 2 and 7 (50%) patients of Group 3 ($p = 0.38$).

Prednisolone was administered as the initial therapy in 69 (88%) patients of Groups 2 and 3. The initial prednisolone equivalent dose of steroid was 30–40 mg daily in 52 (67%), and 60 mg of higher only in 8 (10%) patients (Table 4). The median duration of the initial dose was 10 (range, 2–64) days, and the dose was reduced within 14 days in 57 (77%) patients. The median duration of steroid therapy was 10 (range, 2–28) weeks (Table 4). Steroid pulse therapy (methylprednisolone 1000 mg daily for three days) was administered as the initial therapy in one patient, and as salvage therapy in six patients at the time of pneumonitis aggravation. Among the seven patients, six died of respiratory failure due to progressive radiation pneumonitis.

Outcome of steroid therapy was evaluated in 76 patients (Fig. 1). Symptomatic relief was obtained and the steroid dose was reduced in 71 (93%) of the 76 patients, while no effect was noted in the remaining five patients, who all died of radiation pneumonitis despite escalated steroid administration. Of the 71 patients, 15 (21%) developed recurrent symptoms at the median daily prednisolone dose of 20 mg (range, 10–40 mg) within median 33 days (range, 21–42 days) from the start of the steroid therapy, and required steroids to be escalated. Of the 15 patients, nine died of radiation pneumonitis and one died of complication of steroid therapy. A total of 54 (71%) patients were in remission from pneumonitis and steroid therapy was terminated. The remainder 22 patients died during steroid therapy, 14 of radiation pneumonitis, two of infectious complication (bacterial pneumonia in one, and lung aspergillosis in another patient), five of lung cancer progression, and one of hemoptysis. Thus, 16 patients, who accounted for 4.2% of 385 patients receiving 50–70 Gy of thoracic radiotherapy, and who accounted for 21% of 78 patients treated with steroid therapy, died of radiation pneumonitis or complication associated with steroid therapy. Median survival from the start of steroid therapy in these patients was 45 (range, 8–107) days.

Discussion

Patients with radiation-induced lung injury have been managed in compliance with the expert opinions, because there has been no case series or clinical trial report on clinical course and corticosteroid use for this lung injury. This

Table 4
Corticosteroid, dose and duration of steroid therapy

	N (%)
Corticosteroid	
Prednisolone	69 (88)
Dexamethasone	4 (5)
Betamethasone	4 (5)
Methylprednisolone	1 (1)
Initial dose, mg/body daily (prednisolone equivalent)	
Pulse therapy	1 (1)
60	7 (9)
50	1 (1)
40	10 (13)
30	42 (54)
10–25	17 (22)
Duration of the initial dose, days	
Median (range)	10 (2–64)
≤14	57 (77)
15–28	9 (12)
29≤	8 (11)
Not evaluable	4
Total duration of steroid therapy, weeks	
Median (range)	10 (2–28)
<6	16 (30)
6.1–12	19 (35)
12.1–18	14 (26)
18.1≤	5 (9)
Not evaluable	24

study is the first systemic review of these patients both who received corticosteroid therapy and who did not. Comparison between the expert opinions and the results of this study is given below. First, radiation-induced lung injury is severer when a radiographic change appears earlier [5]. In this study, the initial change in a chest X-ray film was observed in 9.9 (range, −3 to 45) weeks in Group 1, in 6.7 (range, 0–25) weeks in Group 2, and 2.4 (range, 0–10) weeks in Group 3 after the end of thoracic radiotherapy. If patients present with symptoms, presumably they receive a chest X-ray. Thus, the patients with symptoms may have radiographic findings seen sooner, since they receive an X-ray when they complain of symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was longer in Group 1 than that in groups 2 and 3. The difference, however, was negligibly small when compared with the difference in duration between the end of radiotherapy and the first radiographic change. Second, steroid administration is determined generally based on the severity of symptoms [5]. In this study steroid was used when patients developed dyspnea or fever. Dyspnea has been thought to be the cardinal symptom of radiation pneumonitis but fever to be unusual [5,10]. In this study, however, fever was highly associated with fatal radiation pneumonitis; fever was noted in 12% patients of Group 1, in 58% patients of Group 2, and 86% patients of Group 3. This study failed to show utility of blood gas analysis. An oxygen content in the blood was decreased moderately to severely in only 28 (36%) patients in Groups 2 and 3, and did not differ between the two groups. The oxygen content in Group 1 was measured in only small number of patients, and therefore it was not evaluable in this study. Third, 30–100 mg/day of prednisolone has been recommended as the initial dose [4–6,10]. In our practice, a dose of 30–40 mg was the most frequently used. We selected this relatively low dose of steroid mostly because steroid therapy was started in out patient clinic. Forth, duration of the initial dose was within two weeks in 73% of patients, which is consistent to most expert opinions [6,10]. In contrast, tapering schedules varied between a pa-

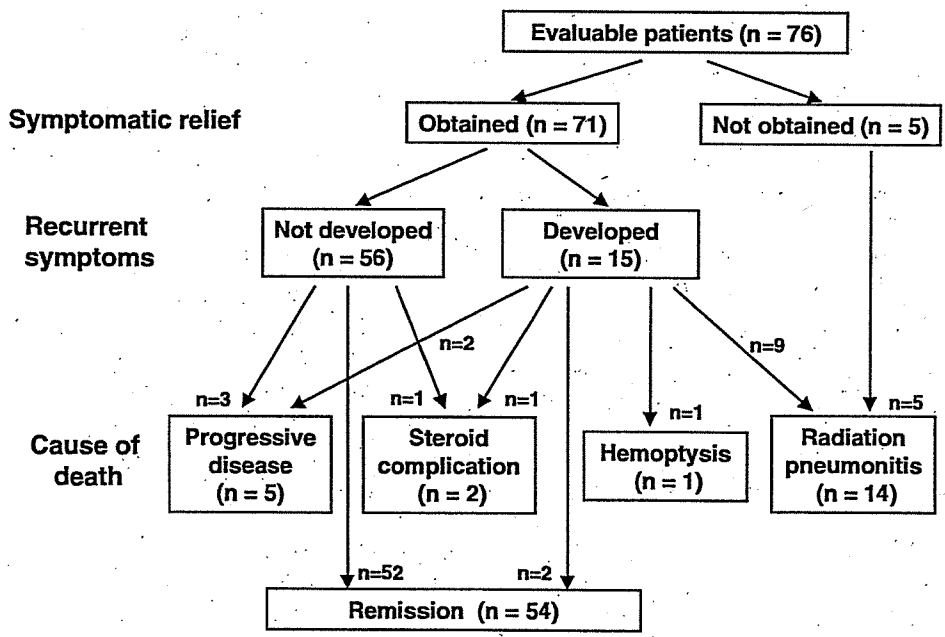

Fig. 1. Outcome of patients who received steroid therapy. Two patients were excluded because of loss of follow-up. Of 76 evaluable patients, 71 (93%) experienced symptomatic relief by steroid therapy.

tient and another in this study. This may be partly due to the diversity in clinical course of radiation pneumonitis, but mostly due to lacking in available recommendation for tapering schedules. In this study, median total duration of steroid therapy was 10 weeks, which may be a tentative guide. A guideline of taper schedule appeared in the latest textbook: the dose should be tapered by 10 mg every two weeks, and be terminated in 12 weeks [10].

Although our clinical practice mostly followed the expert opinions on the management of radiation-induced lung injury as mentioned above, there is little evidence that our steroid use, dose and duration for radiation-induced lung injury were correct. In this study, 21% of patients received steroid therapy and 4% of patients died of radiation pneumonitis among lung cancer patients treated with thoracic radiotherapy at a total dose of 50 Gy or higher. These figures are comparable to the incidence of grade 3 pneumonitis, 3–20%, and that of fatal pneumonitis, 1–4%, in other reports [10].

In conclusion, development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily for two weeks followed by slow taper was selected for the treatment in many patients.

Acknowledgements

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan. We thank Yuko Yabe and Mika Nagai for preparation of the manuscript.

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Received 11 October 2005; received in revised form 19 April 2006; accepted 23 May 2006; Available online 3 July 2006

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