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doi:10.1186/1748-717X-9-51
Cite this article as: Miyata *et al.*: The roles of platelet-derived growth factors and their receptors in brain radiation necrosis. *Radiation Oncology* 2014 9:51.

定位的放射線治療
18：43〜49，2014

悪性神経膠腫の放射線治療後再発例に対するホウ素中性子捕捉療法の成績

Clinical results of boron neutron capture therapy on previously irrediated patients with recurrent malignant glioma

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要旨：ホウ素中性子捕捉療法 (BNCT) は、ホウ素 (^{10}B) が中性子を捕獲し、細胞レベルで生じた核反応から得られる粒子線を利用した腫瘍選択的治療法である。

放射線治療歴を有した34例の再発悪性神経膠腫を対象に検討を行った。再発悪性神経膠腫に対する標準的治療法は確立されておらず、解析は予後因子別解析を利用して行った。

全生存期間中央値は11.2 (8.9-12.4) ヶ月であり、予後不良とされるサブグループでは11.0ヶ月と良好であった (vs 4.4)。予後因子は、BNCT時の組織診断、ステロイド・テモゾロミド治療歴、腫瘍局在 (左右) となり、腫瘍サイズはリスクとはならなかった。

BNCTは原子炉を利用するという障壁により、広く受け入れられるに至らなかった。近年、加速器を中性子源としたBNCT治療装置が開発され、第一相試験が進行中である。本報告では、同様な対象症例に対する原子炉BNCTの良好な治療成績が示された。

key words：神経膠腫、再発、ホウ素中性子捕捉療法、放射線治療、再照射

はじめに

放射線治療後の再発悪性神経膠腫に対しても積極的に放射線治療が行われ成績を上げているが、これまでの報告ではその効果は限定的であり、より効果的かつ安全な照射法が望まれる。ホウ素中性子捕捉療法 (BNCT) は、ホウ素 (^{10}B) が中性子を効率よく捕獲し､生じた核反応から得られる粒子線が細胞一個に相当する飛程で全エネルギーを放出することを利用した高LET (Linear Energy Transfer､線エネルギー付与) の腫瘍選択的治療法である (figure 1) [1)]。

I. 対象と方法

原子炉中性子源を用いたBNCTで治療を実施した再発悪性神経膠腫に対し、後方視的に解析を加えた。本解析の対象となった患者は、当施設で治療を行った再発悪性神経膠腫症例34例で、男性22例、女性12例である。BNCT治療時の平均年齢は50.5 (15〜74) 歳で、全例

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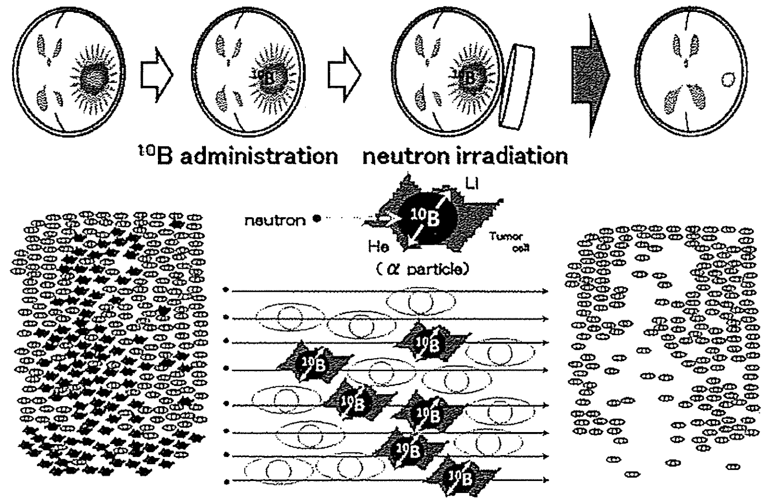

Figure 1 The principle of boron neutron capture therapy (BNCT).
BNCT is a binary approach: A boron-10 (^{10}B)-labeled compound is administered that delivers high concentrations of ^{10}B to the target tumor relative to surrounding normal tissues. This is followed by irradiation with thermal neutrons or epithermal neutrons that become thermalized at depth in tissues. About one cell size level short range high energy of the alpha and ^{7}Li particles released from the ^{10}B (n, alpha) ^{7}Li neutron capture reaction make tumor selective killing without damage for adjacent normal brain tissue.

が初発時もしくは再発／悪性転化時にX線分割外照射を中心とした放射線治療を受けている。照射時のKPS (Karnofsky Performance Status) の中央値は80 (50～100) で、画像上の再発腫瘍体積は平均32mLであった。

BNCTは、熱外中性子による非開頭照射で行い、照射前に実施したBNCT用の治療薬であるホウ素化合物 (BPA; borono-phenylalanine) をトレーサーとしたPET (^{18}F-BPA PET) 検査によるホウ素化合物の集積比および治療当日の血中ホウ素濃度から個々の患者の線量計画を行った (Figure 2) [2]。中性子源としては、主として京都大学原子炉実験所（大阪府・熊取）KURRIを利用し、メンテナンス等の事由で使用不可の期間に関しては日本原子力開発研究機構（茨城県・東海）JRR-4を利用して行った。

また予後因子の解析に際しては、2007年にNABTT (New Approaches to Brain Tumor Therapy CNS Consortium) からJournal of Clinical Oncologyに報告された再発悪性膠腫に対するRPA (recursive partitioning analysis) 分類で用いられた予後因子 (Table 1) [3]を中心に、BNCTにおいて考慮すべき項目を含め検討した。すべての統計解析はJMP Pro 9 (SAS Institute Japan) を使用し行った。

II. 結果

対象患者全体でのBNCT後の生存期間中央値 (MST; median survival time) は、11.2 (95%CI: 8.9 – 12.4) ヶ月であった。今回の解析対象とした項目は、年齢、性別、BNCT時のKPS、初発時の組織型、再発時の組織型、腫瘍局在、ステロイド使用歴、テモゾロミド治療歴、腫瘍体積である。

単一の項目で予後と有意に相関した因子は、BNCT時の組織型（膠芽腫 (glioblastoma、GB) 10.3ヶ月、非GB 15.0ヶ月、$p = 0.045$)、ステロイド使用（使用例 9.6ヶ月、非使用例 12.8ヶ月)、テモゾロミド治療歴（あり 10.3ヶ月、なし

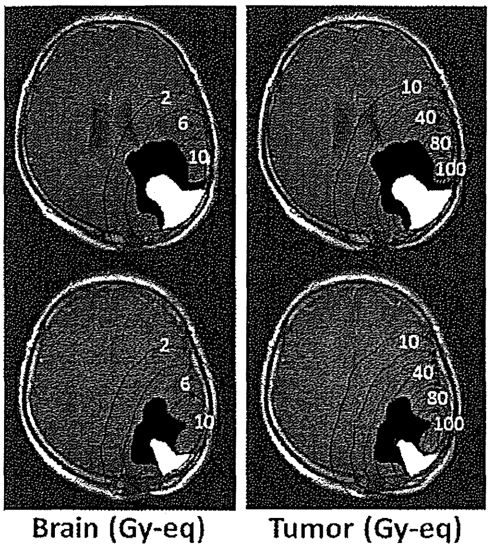

Figure 2 Dose planning of boron neutron capture therapy (BNCT).

Dose planning of neutron capture therapy for the tumor (right) and for the normal brain (left). (Gy-Eq: gray equivalent, star: air instillation to the tumor removed cavity)
In this case, tumor volume was 70mL (black area; tumor; white area; cavity with fluid) and >40Gy was irradiated for 75% and >30Gy for 87% of gross tumor volume. Peak dose for normal brain and skin was 11 and 7 Gy-eq, respectively.

12.4ヶ月)、腫瘍局在 (左半球 8.6ヶ月、右半球 11.7ヶ月) であった。年齢、BNCT時のKPSに関しては、予後に対してカットオフは得られず、また対照としたNABTT-RPAで示された病変の前頭葉限局 (Risk Ratio 1.88, 95% CI: 1.36 - 2.60 p=.0001) [3]に関してもBNCT治療例においては有意な相関は得られなかった (前頭葉限局 10.3ヶ月、それ以外 11.3ヶ月、p=0.131)。腫瘍体積に関しては、カットオフとなった8mL未満の例 (n=7) でMST = 12.8ヶ月、8mL以上の例で11.0ヶ月となり両者に有意差は無かった。中央値である32mL以上の患者 (平均腫瘍体積は52mL) のMSTは 11.4ヶ月であった。また再発時の組織型をGBに限ると、平均腫瘍体積は36mLであり、MSTは 10.4ヶ月であった (Table 2)。

最終的なNABTT-RPAクラス別の解析では、最も予後不良とされたclass 3 + 7でのMST = 4.4 (3.6 – 5.4ヶ月) ヶ月 (Table 1) [3]に対し、BNCT治療群は11.0ヶ月 (7.8 – 11.6ヶ月) となった。

III. 考察

再発悪性神経膠腫の予後は極めて不良であり、特に既放射線治療例での治療には難渋する。手術や放射線の追加・再照射も行われてきたが、再発からの生存期間は6ヶ月程度とされる。我々はこれまでにも、初発・再発の悪性神経膠腫や悪性髄膜腫に対する効果を示してきたが[4,5,6]、既放射線治療の再発例におけるBNCTの治療効果も良好で、当施設ではこれまで他の治療法では得られ難い画像上の縮小効果も報告してきた[7-9]。

脳実質内に浸潤性に発育する悪性脳腫瘍、特に悪性神経膠腫は、浸潤領域の脳細胞が機能していると考えられ、腫瘍を細胞レベルで標的とする選択的治療が理想となる。ホウ素中性子捕捉療法 (boron neutron capture therapy; BNCT) は、生物学的に腫瘍細胞を標的とする粒子線治療であり、浸潤性発育を特徴とする外科的治癒切除が不能な腫瘍に対する治療効果が期待される[10]。BNCTの骨子は、腫瘍細胞にホウ素－10 (boron-10、^{10}B) 化合物を取り込ませた後に患部に中性子を照射することにより、高LETのα粒子が腫瘍細胞ひとつ分に相当する飛程 (約10μm) で放出されることによってホウ素が集積した腫瘍細胞のみを選択的に破壊するという、細胞生物学的な標的手法にある。特筆すべきは、投与するホウ素化合物および照射する中性子が、各々単一では細胞障害性が極めて低いことで、両者が相まって始めて殺細胞効果を示すbinary approachであることである[1]。

BNCTは細胞レベルで選択性を有することから、正常組織内に浸潤性に発育する腫瘍や周囲正常臓器に混在した癌に対する治療効果が期待され、これまでにも多数の臨床試験・研究が行われてきた[11]。あらゆる治療に抵抗性を示し、有効な治療手段の限られる神経膠

腫、特に神経膠芽腫（WHOグレード4）においては期待が高く、これまでにBNCTで治療がなされた症例の多くは初発の悪性神経膠腫であった。

Table 1 Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the NABTTclinical trials

class	results of the recursive partitioning analysis (RPA).	survival time (median)	
1	Initial histology = Not GB, KPS = 80-100, location (Frontal only)	25.7	months
2	Initial histology = Not GB, KPS = 80-100, location (Other)	17.2	months
3	Initial histology = Not GB, KPS = 60-70	3.8	months
4	Initial histology = GB, Age < 50, KPS = 90-100	10.4	months
5	Initial histology = GB, Age < 50, KPS = 60-80	5.6	months
6	Initial histology = GB, Age >= 50, Steroids (No)	6.4	months
7	Initial histology = GB, Age >= 50, Steroids (Yes)	4.9	months

GB, glioblastoma; KPS, Karnofsky performance score.
*Carson et al, J Clin Oncol 25: 2601-6, 2007 [2)]

Table 2 Overview of re-irradiation for recurrent malignant gliomas with large targeted volumes

	no of cases	Irradiation	tumor volume (median, mL)	overall survival (median)	
Cho et al., 1999 (12)	27 GB / 19 grade III	SRS	10	11	months
	15 GB / 10 grade III	fractionated SRT	25	12	months
Lederman et al., 2000 (13)	88 GB	hypofractionated SRT	33	7.0	months
(	38 GB		<30	9.4	months)
(	50 GB		>30	5.7	months)
					months
Voynov et al., 2002 (14)	5 GB / 5 grade III	IMRT	35	10.1	months
Hall et al., 1995 (15)	26 GB / 9 grade III	SRS	28	8.0	months
Combs et al., 2005 (16)	53 GB	fractionated SRT	48	8	months
Patel et al., 2009 (17)	10 GB	fractionated SRT	51	7.5	months
Kawabata et al, present series	26 GB	BNCT	36	10.3	months

abbreviations: GB, glioblastoma; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; IMRT, intensity-modulated radiotherapy; BNCT, boron neutron capture therapy

当施設が利用する京都大学原子炉実験所(KURRI)では、1990年から悪性神経膠腫に対する治療が行われたが、多くの再発例を含みながらも3年生存率で20%以上と従来の治療に比べ約2倍に向上した[12]。しかし当時利用されていた熱中性子では深部での十分な線量が得られず、さらなる改善が必要であると考えられていた。その後中性子およびホウ素化合物が改良され、脳腫瘍以外の癌に対しても良好な成績が示されるに至った[11]。

今回我々が示した再発悪性神経膠腫に対する治療成績は、BNCTからのMSTが約11ヶ月と良好であるが、再発神経膠腫には比較対象となる標準治療群が存在せず、この数値のみをもって有効とするには無理がある。そこでこのBNCTによる治療成績を、再発悪性神経膠腫の臨床試験(NABTTの10個のphase I, IIに登録された333例の解析[3])から得られた予後因子による分類と比較した。これによると、最も予後不良とされたclass 3＋7でのMST 4.4 (3.6 – 5.4) ヶ月[3]に対し、BNCT治療群は11.0 (7.8 – 11.6) ヶ月と大きく上回っていた。BNCTはこれまでに予後不良、すなわち治療に難渋する患者群に対しその効果が非常に高いことが示され、これは初発の膠芽腫症例に対するBNCTでも同様にみられた現象である[13]。

再発悪性神経膠腫に対する再照射治療として、定位的照射が良好な成績を示してきたが、照射法の特徴から標的腫瘍体積に制限がかかる (Table 2) [14-19]。再発後のMSTは定位的照射において10ヶ月以上の成績を示すものも多いが、試験対象とする適格基準にも見られるように、腫瘍体積が比較的小さいものに限られる。腫瘍体積の大きい例に対しても、安全性を確保しつつ腫瘍に対し高線量を付与可能な分割による定位的照射が行われている。しかしながら腫瘍体積が大きいものでは成績が劣る傾向があり、この点においてBNCTはより有利と考えられる。過去の報告例でみると、やはり一回照射のSRS (stereotactic radiosurgery) には限界が見える。比較的腫瘍体積の小さなものでは非常に有効な手段と考えるが[14]、多くの再発例でみられる大きな腫瘍になると、定位的照射法では腫瘍に付与可能な線量に制限があり、生存期間の延長効果はわずかとなる[17]。分割によってより安全な高線量照射が可能となっているが、GBに限った試験でのMSTは7～8ヶ月と劣り、やはり腫瘍体積に影響されている[15,18,19]。BNCTにおいても腫瘍体積8mLが最も良いカットオフと算出され、8mL以上の例でのMSTが12.8ヶ月、8mL未満の例では11.0ヶ月と小さい腫瘍の群で若干高い効果がみられたが、両者に有意差は無い。また中央値32mL以上(平均腫瘍体積は52mL)のMSTは 11.4ヶ月であり、大きな腫瘍に対しても高い治療効果が示された。

BNCTは、悪性神経膠腫の放射線治療後再発例に対し、安全に施行しうる有効な治療手段であり、生命予後を改善した。腫瘍選択的照射であるBNCTでは、特に予後不良とされるサブグループ・治療困難例において有効性が高い傾向が見られた。

IV. 結語

我々の改良型BNCTによる再発悪性神経膠腫の治療では、特に予後不良とされるグループにおいて高い治療効果が示された。悪性神経膠腫のごとく浸潤性に発育する腫瘍では、周囲組織への影響が懸念されるが、BNCTは細胞選択的粒子線治療という特徴から、正常細胞への影響が少なく高線量による強力な放射線照射が可能となるためと考える。

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Clinical results of boron neutron capture therapy on previously irrediated patients with recurrent malignant glioma

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Abstract: We have applied tumor selective particle irradiation known as boron neutron capture therapy (BNCT) using the nuclear reaction ($^{10}B[n, alpha]^{7}Li$) to recurrent malignant gliomas (MGs).

We have treated 34 cases of previously irradiated recurrent MGs with BNCT. As there has been no standard treatment for recurrent MGs so far, it has been difficult to evaluate the results of BNCT. Here we introduce the survival benefit of BNCT for recurrent MGs with RPA classification (NABTT, *J Clin Oncol.* 2007).

The median overall survival (OS) was 11.2 (8.9-12.4) months. In the subgroup considered to be a poor prognosis, OS was satisfactory with 11.0 (7.8-11.6) months (*v.s.* 4.4 (3.6-5.4)). The prognostic factor in our experienced cases did not become the tumor size which was on-site histology, steroids / temozolomide history, tumor location (right < left) with the risk.

Earlier BNCT did not become received widely by a problem to use a nuclear reactor as a neutron source. In late years, a technical problem was solved, and clinical trials using the accelerator based BNCT device have been started. In this report, the treatment result with good clinical results of reactor based BNCT for a similar target cases were shown.

key words: glioma, boron neutron capture therapy, recurrence, reirradiation

ホウ素中性子捕捉療法(Boron neutron capture therapy；BNCT)

川端信司　平松亮　宮武伸一

はじめに

悪性神経膠腫の治療において最大の難題となるのは，正常脳組織に浸潤性に存在する腫瘍細胞であり，これを治療の標的としなければ再発は免れない．腫瘍の画像上の造影域を手術で全て摘出し得ても，周囲脳の浸潤細胞からの再発が必発で，治療には放射線・化学療法を組み合わせた集学的治療が必須となる．放射線治療は非常に有効な治療法であるが，画像診断をもとに治療医が治療計画を行う定位的照射は，開頭手術における治療計画と同様，浸潤部からの再発や正常脳の損傷が問題となる．ホウ素中性子捕捉療法(BNCT；boron neutron capture therapy)は，局所高線量による放射線治療という性格を有しながら，腫瘍を細胞レベルで生物学的に標的とし，正常脳に浸潤した腫瘍細胞をも選択的に治療できるという“細胞選択的粒子線治療”であり，画期的な治療法として注目される[1,2]．

BNCTの原理・背景

ホウ素の同位体である^{10}B(boron-10)が中性子と核反応を生じ，そこから生じたヘリウム原子核(アルファ粒子)とリチウム反跳核により腫瘍細胞を破壊する“ホウ素中性子捕捉療法(BNCT)”の理論が提唱されたのは，中性子発見から間もない1936年のことである．この反応は非常に弱いエネルギーの中性子で得られ，しかも生じるこれらの粒子の飛程がほぼ腫瘍細胞一つ分に相当するため，腫瘍細胞のみが選択的に破壊されるわけである．大量の中性子線や腫瘍選択性のホウ素化合物を必要とし，当時は夢のような治療であった．

BNCTの骨子は腫瘍細胞に^{10}B化合物を取り込ませ中性子を照射することにより，高LET(linear energy transfer；線エネルギー付与)のアルファ粒子が腫瘍細胞一つ分に相当する飛程で放出されることによって，ホウ素が集積した腫瘍細胞のみを選択的に破壊するという細胞生物学的な標的手法にある．特筆すべきは，投与するホウ素化合物および照射する中性子が各々単一では無害であることで，両者が相まって初めて殺細胞効果を示すbinary approach(バイナリーアプローチ)であることである．この反応を中性子捕獲反応といい，中性子捕獲反応は下記の式で表される．

n＋10B→11B→4He＋7LI あるいは 10B(n, α)7Li

この反応によって生じるヘリウム原子核，リチウム反跳核は分裂後それぞれ9 μm，4 μmと腫瘍細胞1個の大きさ以下の距離(飛程)を動き停止し，その間に全運動エネルギーを放出する高LET放射線であり，殺細胞効果が非常に高いというわけである(図1)．

脳実質内に浸潤性に発育する悪性脳腫瘍は浸潤領域の脳細胞が機能していると考えられ，腫瘍を細胞レベルで標的とする選択的治療は理想となる．BNCTは，浸潤性発育を特徴とする外科的治癒切除が不能な腫瘍に対する治療効果が期待され，臨床試験・研究が行われてきた．あらゆる治療に抵抗性を示し，有効な治療手段の限られる悪性グリオーマ(神経膠腫)，特にグリオブラストーマ(神経膠芽腫，WHOグレードⅣ)においては期待が高く，これまでにBNCTで治療がなされた症例の多くは悪性グリオーマである[2]．

BNCTによるグリオーマの治療成績

BNCTの原理が提唱されて以後，臨床応用へ向けた開発研究が進められてきた．その結果，米国では1951年には医療照射用原子炉〔ブルックヘブン国立研究所(BNL)研究炉〕が作られ，1953年から脳腫瘍患者に対するBNCTが開始された．BNLおよびその後のマサチューセッツ工科大学炉(MITR)での臨床研究は1961年に終了したが，当時のホウ素化合物が腫瘍選択性に乏しかったこと，試験に用いられた熱中性子線は組織深達性が悪かったことなどの課題があり，そのため血中ホウ素濃度は高く，正常組織の障害も高頻度であった[1]．その後改良が行われ，米国では単剤のホウ素化合物(BPA；boronophenylalanine)を用い，組織深達性で勝る熱外中性子を用いた非開頭照射が1999年まで行われたが，生存期間は13〜15ヵ月と治療効果はわずかであり，中性子照射線量の増加試験では生存期間が延長したが深刻な中枢神経合併症が生じ[3]，現在米国でのBNCTは困難となっている．欧州においては，これまでにオランダ，チェコでのBSH(sodium borocaptate)を用いた臨床試験，スウェーデン，フィンランドでのBPAを用いた臨床試験などがある[2]．スウェーデンのグループは，BPAの投与量増量・長時間持続投薬(BPA 900 mg/kg)によるプロトコールを導入し，これによってより均一かつ高濃度のホウ素を腫瘍に集積させ，治療成績の向上を示している．2001〜2003年に本手法で新規診断膠芽腫を治療し，生存期間中央値(MST)が17.7ヵ月と，BNLの成績〔BPA(250〜330 mg/kg)，MST 12.8ヵ月〕[3]に比較して有意に良好な成績であったと報告し，同一のホウ素化合物でも投薬プロトコールにより異なった治療成績となることが示された[12]．また同時に，BNCTにおいてもテモゾロミドを併用

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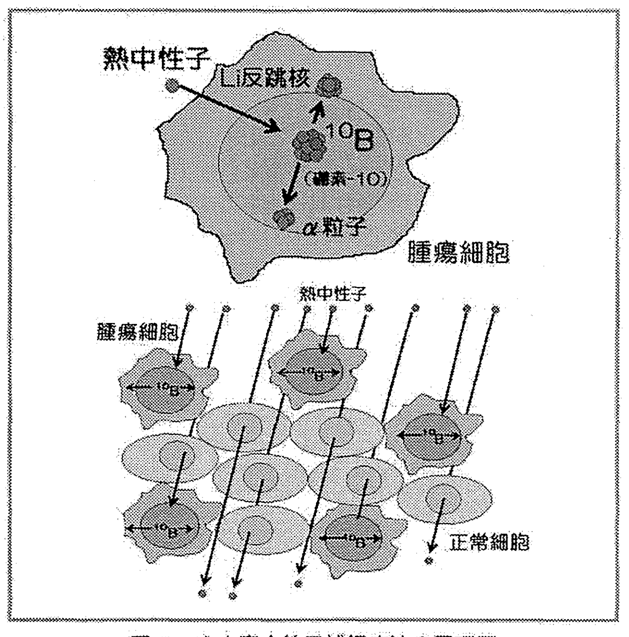

図 1　ホウ素中性子捕捉療法の原理図

BNCT では腫瘍選択性を有するホウ素(^{10}B)化合物を投与し，低エネルギーの中性子を照射することで^{10}B が中性子と核反応を生じ，そこから生じたヘリウム原子核(アルファ粒子)とリチウム反跳核で腫瘍細胞の選択的破壊を実現する．ホウ素化合物が選択的に腫瘍に充分集積し，かつ正常脳・血中の濃度が低下した時点で患部に中性子を照射すれば，腫瘍のみが浸潤部においても選択的に破壊される．

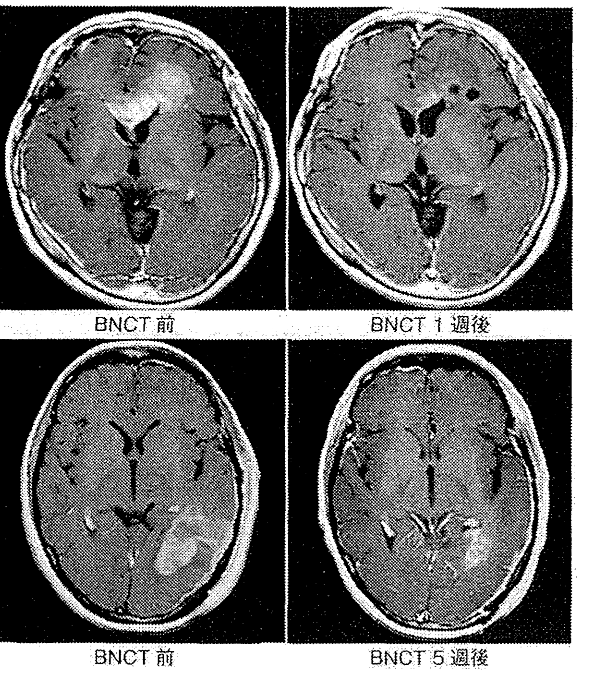

図 2　ホウ素中性子捕捉療法の治療効果

熱外中性子を用いた非開頭 BNCT に，集積機序の異なる 2 種類のホウ素化合物(BPA，BSH)を併用したプロトコールでの治療例．治療後早期から造影 MRI 画像上増強効果を示す腫瘍の縮小効果を認め，非常に良好な局所制御が得られた．

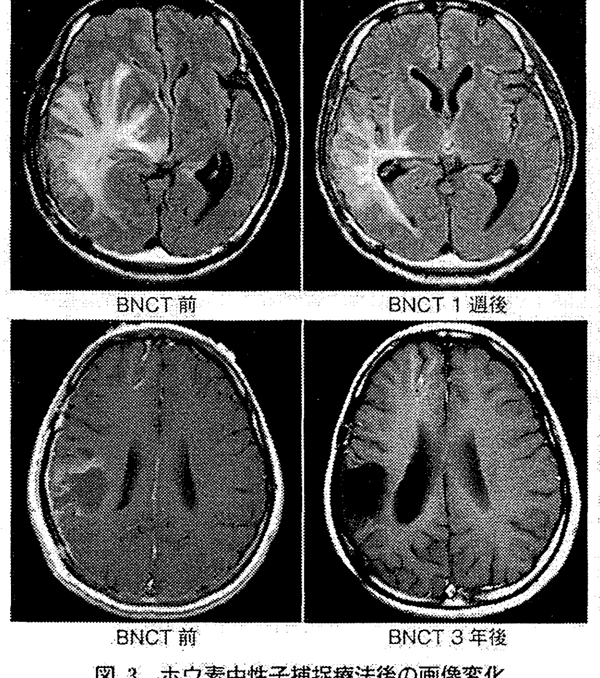

図 3　ホウ素中性子捕捉療法後の画像変化

BNCT 後早期から，ステロイド剤や浸透圧利尿剤等を用いなかったが，MRI(FLAIR)画像上の高信号病変は縮小し，それに伴って神経脱落症状の改善が得られた(上段)．また，外科的全摘出を実施した例(下段)でも長期間局所再発はなく，照射後の周囲脳の変化はほとんどみられない．

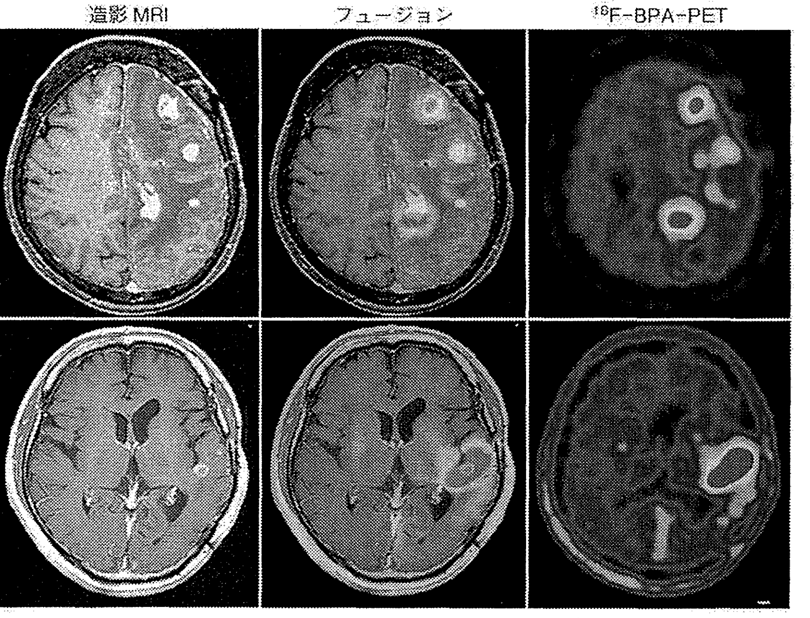

図 4　BPA(ホウ素フェニルアラニン)をトレーサーとした^{18}F-BPA-PET 画像

多発性の病変においても，病変部を含めた中性子照射野を設定することで，ホウ素化合物の集積に合わせて 1 回の治療ですべてに高線量が照射できる(上段)．また，MRI でのガドリニウム増強を受ける腫瘍塊を超えて^{18}F-BPA-PET で周辺の非造影部にも高集積がみられる例を経験するが，このような例においてもホウ素化合物の分布によって高線量が照射され，この部を含めた照射野を設定する以外，特別な工夫は不要である(下段)．

することで治療成績が向上することが示されたが，実際にはテモゾロミド抵抗性を示す患者群におけるBNCTの有用性が期待されるものの，テモゾロミド反応性の患者群においては積極的な併用療法が推奨される[13]．

本邦でも1968年から日本原子力研究開発機構等でBNCTが行われるようになり，Nakagawaらは149例の神経膠腫に対しBSH単剤による開頭術中，中性子照射を行い，膠芽腫のMSTは21.3ヵ月と高い効果を報告している[10]．京都大学原子炉実験所では1990年から悪性神経膠腫に対する治療が行われたが，多くの再発例を含みながらも，3年生存率で20%以上と従来の治療に比べ約2倍に向上したが，欧米同様多くに課題も残った[15]．現在までに臨床研究で用いられてきたホウ素化合物はBSHとBPAのみであり，これまでの臨床研究では各々が単剤で使用されてきた．BSHには1分子あたりのホウ素含有量が多く，多量のホウ素を送達できるが，分子量が大きく血液脳関門を通過しにくいという問題がある．また，BPAは必須アミノ酸であるフェニルアラニン骨格を有し，アミノ酸代謝の活発な腫瘍細胞に高集積を示すが，腫瘍とコントラストがあるものの正常脳にも分布する点，および細胞周期に依存しやすい点など一長一短がある．われわれは2002年から，熱外中性子を用いた非開頭BNCTにこれら2種類のホウ素化合物を併用し両者の欠点を克服する試みを開始し[6]，新規診断膠芽腫のMSTは15.6ヵ月と，それまでの施設コントロールを有意に上回った．2004年以降われわれは，BPAの増量(700 mg/kg)およびX線分割外照射をBNCTに組み合わせ，MSTが23.5ヵ月と延長することを示した(図2)[7]．X線分割外照射併用プロトコールは他グループでも採用され，最近YamamotoらがBNCTの自験例から，新規診断膠芽腫における開頭・術中照射群と非開頭・外照射群の治療成績を比較し報告している．これによれば，開頭・術中照射群ではBSH単剤を用い，非開頭・外照射群ではBSH，BPA(250 mg/kg)の併用にX線分割外照射を組み合わせ，MSTがそれぞれ23.3ヵ月(N=7)，27.1ヵ月(N=8)と非常に良好である[5,7,14]．これら熱外中性子を用いた国内外の臨床試験の詳細については最近行なったレビューを参照いただきたい[2]．

悪性神経膠腫の再発例となるとさらに難治となり，特に既放射線治療例では治療法の選択に難渋する．新規診断例の標準治療と同様，これまでに手術や放射線の追加照射も行われてきたが，生存期間は約6ヵ月である．再発例においてもBNCTの治療効果は強力で，他の治療法では得られ難い画像上の縮小効果も多くの例で経験する(図3)．最近の再発膠芽腫を対象とした報告によると，BNCT後の生存期間は8.7ヵ月であり[11]，われわれの10.8ヵ月と同等，良好である[9]．

近年の放射線治療装置・技術の進歩は目覚ましいが，画像誘導下に照射計画を行い，それによって計画された領域内すべての組織が照射を受ける点は共通した問題点である．BNCTでは画像上造影効果を示した病変を照射野内に含めたとしても，ホウ素化合物が高集積しなければ線量が付与されず，例えば治療後の画像に混在する壊死巣やその周囲の正常脳への再照射・被曝は最小限にとどまることになる．これを効率よく視覚化するのがわれわれが積極的に導入する^{18}F-BPA-PET(図4)ということになる[4,6,8]．局所高線量による再発例の治療で問題となる十分な治療効果(線量付与)と周囲や内部に存在するリスク組織への線量低減といったジレンマが，BNCTではその生物学的選択性により解消されると考えられ，他の治療法と比べても安全性を維持しつつ治療効果が発揮できる理由と思われる(図2，3)．

加速器を中性子源とするBNCTの可能性

BNCTを取り巻く最近の話題としては加速器を中性子源としたBNCTの開発である．BNCTが医療として認知されるには原子炉から脱却しなければならない．最近，脳腫瘍での成績の向上や他臓器への応用など多方面からの注目もあり，加速器中性子源の開発研究に拍車がかかっている．

医療照射に対応可能な加速器中性子源の開発は既に実現しており，医療機器としての申請も不可能ではなくなっている．これによりBNCTはようやく医療承認を目指す治験という枠組みに参入できるようになり，本邦においては世界に先駆けBNCT用加速器中性子源を用い，再発悪性神経膠腫を対象にした第一相臨床試験が現在進行中である．

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Brain Tumor Pathol (2013) 30:67–72
DOI 10.1007/s10014-012-0109-x

ORIGINAL ARTICLE

IDH1 mutation as a potential novel biomarker for distinguishing pseudoprogression from true progression in patients with glioblastoma treated with temozolomide and radiotherapy

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Received: 9 February 2012 / Accepted: 11 June 2012 / Published online: 3 July 2012

Abstract The purpose of this study was to distinguish pseudoprogression (PP) from early true progression in patients with glioblastoma (GBM) based on the presence of a mutation in isocitrate dehydrogenase 1 (IDH1). We retrospectively surveyed 32 patients with GBM or GBM with oligodendroglioma component (GBMO) who underwent biopsy or maximal tumor resection followed by concurrent radiotherapy and temozolomide (TMZ). We then selected patients with early radiological progression in magnetic resonance imaging within 6 months after concurrent radiotherapy and TMZ treatment. DNA was extracted from their tumor blocks. The IDH1 mutation was analyzed in the genomic region by direct sequencing as a biomarker for PP. Twenty-eight patients were diagnosed with GBM and four with GBMO. Eleven patients were discovered to have early radiological progression. PP was detected in two patients (6.3 %) diagnosed with GBMO and one patient with GBM. Both of the GBMO patients with PP had the IDH1 mutation, the one GBM patient with PP and the other eight patients with early true progression with wild type. The sensitivity and specificity of the IDH1 mutation for detecting PP were 66.7 and 100 %, respectively. This study suggests the IDH1 mutation may become a novel molecular biomarker for PP. Analyzing the IDH1 mutation, in the case of recognizing early radiological progression, may enable distinction of PP from early true progression, and we could determine the need for second-look surgery.

Keywords Biomarker · Concurrent radiotherapy and temozolomide · Glioblastoma · IDH1 mutation · Pseudoprogression

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Introduction

Glioblastoma (GBM) is one of the most malignant brain tumors, with patients having a median life expectancy of 13–17 months after diagnosis despite standard treatment of maximal tumor resection and concurrent radiotherapy (RT) and temozolomide (TMZ) followed by six courses of maintenance TMZ [1]. Contrast enhancement on magnetic resonance imaging (MRI) is a standard tool for assessing response to treatment. Recently, there have been increasing numbers of reports of pseudoprogression (PP), which is difficult to distinguish from early true progression (TP) based on contrast enhancement on MRI [2]. There are few effective biomarkers of PP, so many patients may undergo an unnecessary and potentially harmful second surgery. Recently, genome-wide mutational analysis revealed somatic mutations of cytosolic NADP+-dependent isocitrate dehydrogenase 1 (IDH1) in approximately 12 % of GBMs [3]. The IDH1 mutation is associated with a favorable prognosis in adult patients with GBM [3, 4]. Pseudoprogression also indicates a good prognosis [5]. We investigated the incidence of PP according to the IDH1 mutation.

Materials and methods

Patients

Between December 2005 and November 2010, a total of 32 patients with GBM or GBM with oligodendroglioma component (GBMO) who underwent biopsy or maximal tumor resection and treatment with 60 Gy of brain-localized RT concurrent with continuous TMZ (75 mg/m^2/day) followed by maintenance TMZ (150–200 mg/m^2/day for 5 days, every 28 days) were reviewed. All histological slides were re-evaluated by two neuropathologists blinded to the clinical background and outcome of patients, and classified according to the 2007 WHO classification. GBMOs are defined based on histological specimens that identify tumor parts with features of oligodendroglial differentiation within typical histological findings of GBM. The pathological diagnosis did not refer to genetic information.

Clinical, radiographic and pathological records were reviewed. All patients underwent MRI exams (T2, T1, T1 with gadolinium, diffusion-weighted images and fluid attenuated inversion recovery) before and within 48 h after surgery, within 7 days, and every 2 or 3 months after concurrent chemoradiation therapy. Patients with early radiological progression (RP), within 6 months after concurrent treatment, were defined according to MacDonald's criteria on MRI. Pseudoprogression was defined as radiological improvement or stability of lesions without further treatment other than adjuvant TMZ.

IDH1 sequencing and MGMT promotor methylation status assessment

Tumor DNA was extracted from fixed paraffin-embedded tissues using the TAKARA DEXPAT kit (Takara) as follows. After review of hematoxylin-and-eosin-stained slides to confirm normal and neoplastic tissues, then determination was made of where sufficient invasive GBM was present. DNA was also extracted from tumor specimens, quickly frozen and stored at −80 °C using AllPrep DNA/RNA Mini Kit (Qiagen). The genomic region spanning wild-type R132 of IDH1 was analyzed by direct sequencing using the following primers: IDH1 forward 5-TGC AAAATCACATTATTGCC and IDH1 reverse 5-AATGG CTTCTCTGAAGACCG. The PCR products were purified using the LaboPass PCR Purification Kit (COSMO GENETECH). All sequence reactions were carried out using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The reactions were carried out in an automated DNA analyzer (3730xl DNA Analyzer; Applied Biosystems). O6-Methylguanine-DNA methyltransferase (MGMT) promotor methylation status was also evaluated with the methylation-specific polymerase chain reaction (MSP), which was performed as previously described [6].

Statistical analysis

Sensitivity and specificity for detecting PP with IDH1 mutation, pathological diagnosis of GBMO or MGMT promotor methylation status were assessed. Significance of correlations between the parameters was assessed using Fisher's exact test, and values of $P < 0.05$ were considered statistically significant.

Results

Eleven (34.4 %) of 32 patients developed early RP. In these 11 patients with RP, 8 developed true progressions (TP), whereas three patients were classified as having PP (Table 1). Two of 11 patients had an IDH1 mutation, and both mutations were of the R132H type. Two PP patients had an IDH1 mutation, the other patient had wild-type IDH1, and the MGMT promotor methylation status could be determined for two out of three PP patients. Eight patients with early TP had progressive disease, and died or developed terminal disease during the investigation. All early TP patients had wild-type IDH1, but MGMT promotor methylation statuses were various: three patients were methylated, and five were unmethylated (Tables 2, 3). Within early RP group, the sensitivity and specificity of IDH1 mutation for detecting PP were 67 and 100 %, respectively; meanwhile, those of MGMT promotor methylation status were 67 and 63 %, respectively.

Histopathologically, two PP patients were diagnosed with GBMO and one patient with GBM. Meanwhile, seven early TP patients were diagnosed with GBM, and one was diagnosed with GBMO (Table 4). The sensitivity of GBMO was 67 %, but the specificity was 88 %. Using Fisher's exact test, there were no significant associations between the IDH1 mutation and PP ($P = 0.055$) mutations, MGMT methylation status and PP ($P = 0.424$), or GBMO and PP ($P = 0.156$).

Illustrative case

A 44-year-old woman presented with mild hemiparesis on the left side. MRI with contrast media demonstrated a heterogeneously enhanced mass in the right parietal region (Fig. 1a). Surgical resection was performed, and the enhanced lesion was totally removed (Fig. 1b). The tumor was diagnosed as a GBM with an oligodendroglioma component (Fig. 2a, b). Concurrent TMZ and radiotherapy was performed, followed by 5 consecutive days of TMZ

Table 1 Cases developing early radiological progression

Case	Pathological diagnosis	Course	IDH1	MGMT promoter methylation status
1	GBM	True progression	Wild type	Methylated
2	GBM	Pseudoprogression	Wild type	Methylated
3	GBM	True progression	Wild type	Unmethylated
4	GBM	True progression	Wild type	Unmethylated
5	GBM	True progression	Wild type	Unmethylated
6[a]	GBMO	Pseudoprogression	Mutation	Methylated
7	GBM	True progression	Wild type	Methylated
8	GBM	True progression	Wild type	Unmethylated
9	GBMO	True progression	Wild type	Unmethylated
10	GBMO	Pseudoprogression	Mutation	Unmethylated
11	GBM	True progression	Wild type	Methylated

IDH1 isocitrate dehydrogenase 1, *GBM* glioblastoma multiforme, *GBMO* glioblastoma with oligodendroglioma component

[a] Illustrative case

Table 2 Relevance between IDH1 mutation and pseudoprogression

IDH1 mutation	PP	TP
Mutation	2	0
Wild type	1	8
Sensitivity	67 %	
Specificity	100 %	
Fisher's exact test	$P = 0.055$	

Table 3 Relevance between MGMT methylation status and pseudoprogression

MGMT	PP	TP
Methylation	2	3
Unmethylation	1	5
Sensitivity	67 %	
Specificity	63 %	
Fisher's exact test	$P = 0.424$	

Table 4 Relevance between pathological diagnosis and pseudoprogression

Pathological diagnosis	PP	TP
GBMO	2	1
GBM	1	7
Sensitivity	67 %	
Specificity	88 %	
Fisher's exact test	$P = 0.156$	

IDH1 isocitrate dehydrogenase 1, *GBM* glioblastoma multiforme, *GBMO* glioblastoma with oligodendroglioma component, *MGMT* O6-methylguanine-DNA methyltransferase

administered every 28 days. Early radiological progression was found 2 months after the concurrent treatment (Fig. 1c) without clinical deterioration. Spontaneous improvement of the enhancing lesion was observed without further treatment other than adjuvant TMZ after another 2 months (Fig. 1d). By immunohistochemistry, the tumor cells exhibited diffuse IDH1-R132H mutation (Dianova, Hamburg, Germany; monoclonal, Clone H09, diluted 1:50) (Fig. 2c). Her lesion was revealed to have an IDH1 mutation also by direct sequencing (Fig. 2d). This patient has remained free of relapse for more than 3 years.

Discussion

Pseudoprogression was first described by Hoffman et al. [7] in a group of malignant glioma patients treated with RT and carmustine. This phenomenon has been increasingly reported since the standard therapy of concurrent radiation and TMZ was developed [2, 8–11] but the incidence rates of PP vary (5.5–46.7 %) among reports [5, 9, 11–13]. Pseudoprogression is defined as the spontaneous improvement of enhancing lesions without further treatment other than adjuvant TMZ. Some studies have demonstrated that PP is associated with favorable prognosis [5, 8, 13, 14]. Hence, meaningful biomarkers are desired so that TMZ can be used more effectively and in order to avoid unnecessary second-look surgeries for PP. The MGMT promoter methylation status can predict the incidence and outcome of PP [8]. Brandes et al. found that its sensitivity for PP was 66 % and specificity 89 %. Kan et al. reported overexpression of p53 as a potential biomarker for predicting the development of PP. Its sensitivity and specificity were 87.5 and 70 %, respectively [13]. Methylated MGMT

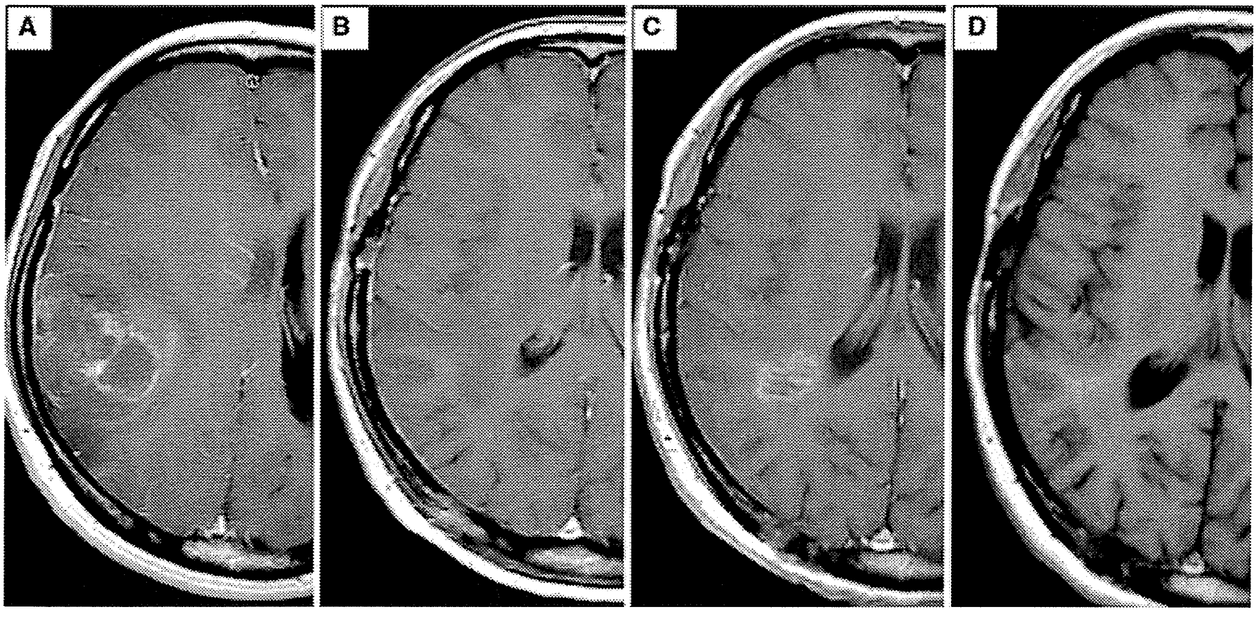

Fig. 1 Pseudoprogression in a 44-year-old woman with a right parietal glioblastoma with an oligodendroglioma component followed by concurrent 60-Gy radiotherapy and temozolomide therapy. Preoperative (a) and postoperative (b) contrast-enhanced MRIs are shown. The gadolinium-enhanced lesion was grossly resected, but early radiological progression was found 2 months after concurrent treatment (c) without clinical deterioration. Spontaneous improvement of the enhancing lesion was observed without further treatment other than adjuvant TMZ after another 2 months (d)

promoter and p53 overexpression are slightly weak biomarkers for distinguishing PP from early true progression in order to decide on courses of treatment. Although GBMO seems a good biomarker, it would be inadequate for making decisions because GBMO could include an early TP case and the diagnosis could fluctuate depending on the pathologist. Some patients might be diagnosed with GBM or anaplastic oligodendroglioma. There are few reports regarding PP and anaplastic gliomas, but Wit et al. [15] described 3 patients with PP out of 32 malignant glioma patients after radiotherapy; two had oligodendroglial features (one anaplastic oligodendroglioma and one anaplastic oligoastrocytoma). Oligodendroglial features may have some influence on developing PP. Regarding the IDH1 mutation, both the sensitivity and specificity for detecting PP were high at 66.7 and 100 %, respectively, within early radiological progression, and this biomarker provides a very objective means of assessment. However, there was no narrowly found statistical significance between the IDH1 mutation and pseudoprogression. If some additional inspections of larger populations revealed high specificity of the IDH1 mutation in pseudoprogression, we could then determine the need for second-look surgery when MRI detected early radiological progression.

Can any possible assumption be made to account for the mechanisms involved in the relationship between the IDH1 mutation and pseudoprogression? Histopathologically, PP resembles radiation necrosis, i.e., a mixture of necrotic changes and gliosis with few viable tumor cells, in addition to endothelial thickening, hyalinization and thrombosis of vessels [5, 11]. Radiation-induced injury to endothelial cells is thought to be a main cause of acute and subacute radiation injury. Endothelial cell death induces destruction of the blood brain barrier (BBB) with vasogenic edema, ischemia and hypoxia [16]. Also, radiographically, PP shows enlarging contrast enhancement and edema on MRI, which suggests destruction of the BBB. The BBB is composed of capillary endothelial cells surrounded by basal lamina and astrocytic perivascular endfeet. Is there any relationship between the IDH1 mutation and MGMT promoter methylation status and blood-brain barrier damage? It is well known that MGMT promoter methylation status and IDH1 mutations in the GBM may sensitize tumors to irradiation and chemotherapy. Therefore, there could be two hypotheses for PP. The first is that the tumor vessels' endothelial cells came from GBM stem cells with methylated MGMT promoter or IDH1 mutation. Wang et al. [17] demonstrated the capability of GBM stem cells for differentiation along tumor and endothelial lineages. If this was correct, and the tumor vessels' endothelial cells also had methylated MGMT promoters or IDH1 mutations, DNA damage could easily increase, and clinically PP could develop. In our cases, immunostaining of IDH1 mutations could not be detected in any type of tumor vessels (Fig. 2c). Then, we state the second

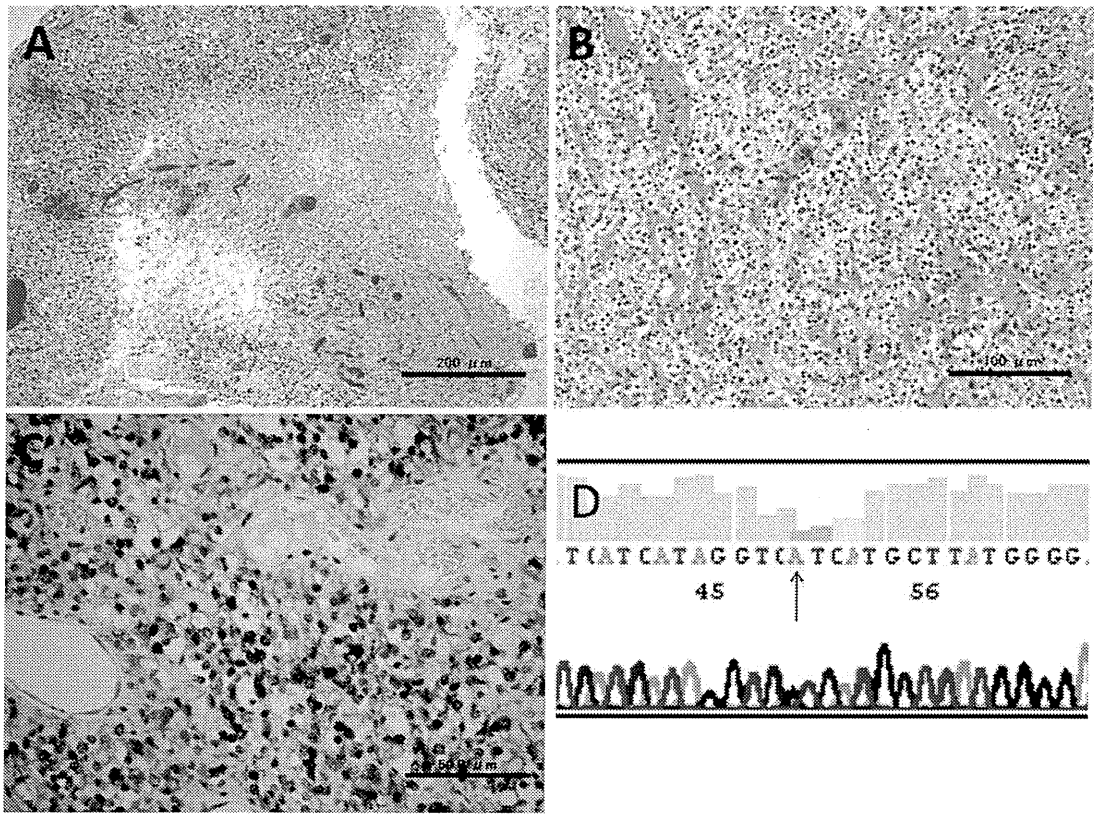

Fig. 2 Pathological findings and molecular biological detection of isocitrate dehydrogenase 1 (IDH1) mutation in a 44-year-old woman with pseudoprogression 2 months after concurrent 60-Gy radiotherapy and temozolomide therapy. Photomicrograph shows necrosis with pseudopalisading pattern (**a**, H&E, ×100), and tumor cells with clear cytoplasm and marked microvascular proliferation (**b**, H&E, ×200). Immunohistochemical examination with H09 (Dianova, Hamburg, Germany; 1:50), which specifically detects the mutant IDH1R132H, showed that almost all tumor cells were diffusely stained except for endothelial cells (**c**). Somatic mutations in IDH1 from CGT to CAT were detected by direct sequencing of tumor DNA (**d**)

hypothesis about PP, in which tumor cells with genetic or epigenetic anomalies, which might maintain the BBB, respond to initial therapy, resulting in the collapse of the BBB, and then PP would develop.

In summary, in our small series, there might be a correlation between PP and an IDH1 mutation. If this correlation were statistically confirmed in larger populations, we could avoid unnecessary and potentially harmful second-look surgery.

Acknowledgments We thank Yumiko Shinohe for assistance with the preparation of paraffin-embedded tissues and the DNA extraction.

Conflict of interest None declared.

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International Journal of
Radiation Oncology
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Clinical Investigation

Phase 2 Trial of Hypofractionated High-Dose Intensity Modulated Radiation Therapy With Concurrent and Adjuvant Temozolomide for Newly Diagnosed Glioblastoma

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Received Sep 14, 2013, and in revised form Dec 5, 2013. Accepted for publication Dec 10, 2013.

Summary

The clinical effect of hypofractionated high-dose intensity modulated radiation therapy with concurrent and adjuvant temozolomide was evaluated in 46 patients with glioblastomas. This treatment was performed without radiation-related adverse events and altered the dominant failure pattern from localized to disseminated. The median survival was 20.0 months. Radiation necrosis was the most frequently observed late toxicity, but necrosis in the subventricular zone was significantly associated with better survival.

Purpose/Objectives: To assess the effect and toxicity of hypofractionated high-dose intensity modulated radiation therapy (IMRT) with concurrent and adjuvant temozolomide (TMZ) in 46 patients with newly diagnosed glioblastoma multiforme (GBM).

Methods and Materials: All patients underwent postsurgical hypofractionated high-dose IMRT. Three layered planning target volumes (PTVs) were contoured. PTV1 was the surgical cavity and residual tumor on T1-weighted magnetic resonance images with 5-mm margins, PTV2 was the area with 15-mm margins surrounding the PTV1, and PTV3 was the high-intensity area on fluid-attenuated inversion recovery images. Irradiation was performed in 8 fractions at total doses of 68, 40, and 32 Gy for PTV1, PTV2, and PTV3, respectively. Concurrent TMZ was given at 75 mg/m^2/day for 42 consecutive days. Adjuvant TMZ was given at 150 to 200 mg/m^2/day for 5 days every 28 days. Overall and progression-free survivals were evaluated.

Results: No acute IMRT-related toxicity was observed. The dominant posttreatment failure pattern was dissemination. During a median follow-up time of 16.3 months (range, 4.3-80.8 months) for all patients and 23.7 months (range, 12.4-80.8 months) for living patients, the median overall survival was 20.0 months after treatment. Radiation necrosis was diagnosed in 20 patients and was observed not only in the high-dose field but also in the subventricular zone (SVZ). Necrosis in the SVZ was significantly correlated with prolonged survival (hazard ratio, 4.08; $P=.007$) but caused deterioration in the performance status of long-term survivors.

Conclusions: Hypofractionated high-dose IMRT with concurrent and adjuvant TMZ altered the dominant failure pattern from localized to disseminated and prolonged the survival of patients with GBM. Necrosis in the SVZ was associated with better patient survival, but the benefit of radiation to this area remains controversial. © 2014 Elsevier Inc.

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Supported by a JSPS KAKENHI grant (grant no. 21591886).
Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–8, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2013.12.011

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor. Surgical removal followed by radiation therapy with concurrent and adjuvant temozolomide (TMZ) is the standard treatment for newly diagnosed GBM. Although TMZ can improve patient outcomes, the prognosis remains poor, and the median survival is only 14.6 months after treatment (1).

The failure pattern after standard treatment is local (2), and intensive treatment targeting localized lesions is required to improve the outcome in patients with GBM. We initiated a phase 2 trial of hypofractionated high-dose intensity modulated radiation therapy (IMRT) with concurrent and adjuvant TMZ for better control of GBM in 2006. In the present study, we investigated the efficacy and safety of our intensive IMRT using TMZ in patients with GBM.

Methods and Materials

Patients

This single-institution prospective study was approved by the ethics committee of our institution. Eligibility criteria included newly diagnosed and pathologically confirmed GBM without an enhanced lesion beside the cerebrospinal fluid (CSF) space on baseline magnetic resonance imaging (MRI), age $\geq$18 years, and normal liver, kidney, and bone marrow function.

Surgical removal

Before registration, surgical tumor removal was performed in all patients. The extent of resection was not part of the inclusion criteria but was calculated by comparing preoperative and postoperative MRI. Gross total resection was defined as removal of $\geq$95% of the enhancing tumor.

The methylation status of the *O-6-methylguanine-DNA methyltransferase (MGMT)* gene promoter was determined by methylation-specific polymerase chain reaction analysis (3).

Hypofractionated high-dose IMRT

Computed tomography (CT) simulation with a 2-mm slice thickness was performed for all patients. MRIs of fluid-attenuated inversion recovery (FLAIR) images and contrast-enhanced T1-weighted images were also obtained before planning and were fused to the simulated CT images for target delineation. A simultaneous integrated boost technique was used to deliver different radiation doses to layered targets. The gross tumor volume (GTV) was defined as the contrast-enhancing residual tumor plus the entire surgical cavity on MRI. The planning target volume 1 (PTV1) was defined as the GTV plus a 5-mm margin, PTV2 as a 15-mm margin surrounding PTV1, and PTV3 as the high-intensity region on FLAIR images without margins. Irradiation was delivered in 8 fractions over 10 days (total dose of 68 Gy in 8.5-Gy fractions to PTV1, 40 Gy in 5.0-Gy fractions to PTV2, and 32 Gy in 4.0-Gy fractions to PTV3). IMRT was performed with either multiple static intensity-modulated beams or intensity-modulated dynamic arcs.

Concurrent and adjuvant chemotherapy

All patients underwent concurrent and adjuvant TMZ. This agent was administrated orally, once daily, at 75 mg/m^2 for 42 consecutive days. This treatment was begun within 1 week after registration, and IMRT was performed during this course of chemotherapy. Adjuvant TMZ was administered at 150 to 200 mg/m^2 orally, once daily, for 5 consecutive days every 28 days, for a total of 12 cycles or until tumor progression.

Patient follow-up

The failure patterns were classified as follows: local (at the regional tumor), distant (intraparenchymal, but distant from the original tumor site), and disseminated (distant from the original tumor and exposed to the CSF space) (Fig. 1). Contrast-enhanced MRI was performed within 14 days before IMRT to obtain baseline images, then at intervals of 1 or 2 months after IMRT. If an enhanced lesion appeared, C^{11}-methionine positron emission tomography (Met-PET) was performed, and the uptake of methionine was semiquantitatively evaluated by the ratio of uptake in the lesion to that in the contralateral normal brain (T/N ratio). Enhancing lesions with a T/N ratio of $>$1.8 were diagnosed as tumor progression, and lesions with a ratio of $\leq$1.8 were diagnosed as radiation necrosis. The lesion was diagnosed as tumor progression regardless of methionine uptake when viable cells were revealed in the specimen at the second surgery. When Met-PET was not available, daily dexamethasone was administered orally, and MRI was performed 4 to 8 weeks later. The lesion was diagnosed as necrosis when it shrunk on MRI but as recurrence in other cases.

Hematologic and nonhematologic toxicities were evaluated monthly. Toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The primary endpoint of this study was overall survival (OS); the secondary endpoints were progression-free survival and safety. Survival curves were drawn by the Kaplan-Meier method, and a 2-sided log—rank test was used for analysis. Cox's proportional hazard model gave estimates for the hazard ratios (HRs). All analyses were performed on an intention-to-treat basis with JAMP software (version 10.0.2).

Results

Patients

Between August 2006 and August 2012, a total of 46 patients were enrolled in this study. Their median age was 65.5 years (range, 40-80 years), and 27 of the 46 patients (59%) were Radiation Therapy Oncology Group recursive partitioning analysis (RTOG RPA) class V or VI. The location of the tumor according to the classification of Lim et al (4) was as follows: group 1 in 18 patients, group 2 in 12, group 3 in 13, and group 4 in 3; the enhanced lesion contacted the subventricular zone (SVZ) in 30 patients (65%). The patient characteristics are summarized in Table 1.

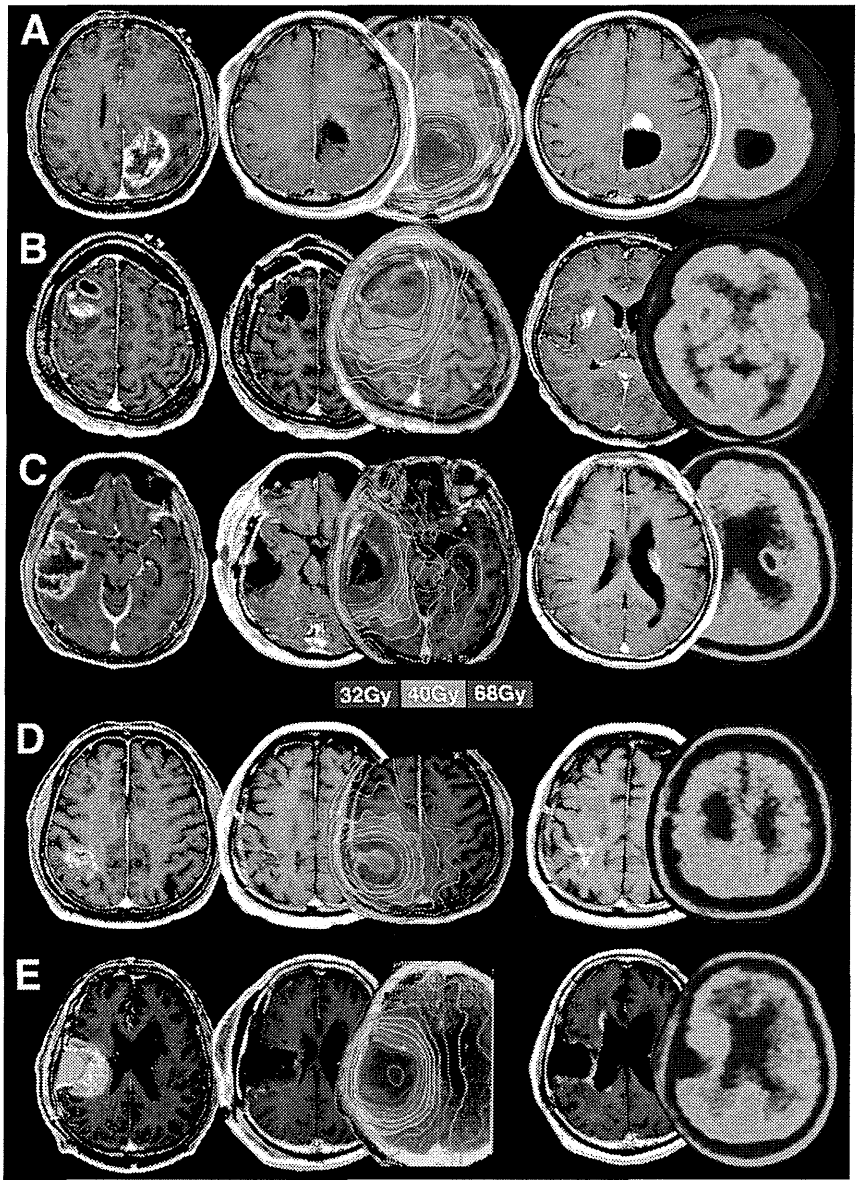

Fig. 1. Failure patterns and radiation necrosis patterns. Three different patterns of failure were evident: local (A), distant (B), and disseminated (C). Two different patterns of radiation necrosis were evident: regional necrosis (D) and necrosis in the subventricular zone (E). Enhanced magnetic resonance imaging (MRI) performed before (left) and after (middle) surgery and at the reappearance of enhanced lesions on MRI was demonstrated with isodose maps and methionine-positron emission tomography.

At the time of the last follow-up visits, the median follow-up periods were 16.3 months (range, 4.3-80.8 months) for all patients and 23.7 months (range, 12.4-80.8 months) for living patients.

Hypofractionated high-dose IMRT

All patients were treated according to the protocol. The median PTV1 was 80.9 cc (range, 26.5-267.2 cc), the median PTV2 was 160.7 cc (range, 78.5-374.3 cc), and the median PTV3 was 0.6 cc (range, 0.0-65.9 cc).

Concurrent and adjuvant TMZ

Temozolomide was administered to all patients concurrently with IMRT but was withdrawn 12 days after initiation in 1 patient because of a grade 3 skin rash. In addition to this patient, adjuvant chemotherapy was abundant in 4 patients because of adverse events of TMZ: grade 3 pneumonitis in 1, grade 3 fatigue in 2, and grade 3 bone marrow suppression in 1. In addition to those 5 patients, TMZ was discontinued in 5 patients because of performance status deterioration. Among the remaining 36 patients, 12 cycles of TMZ were completed without tumor progression in 13