に保護され慎重に取り扱われるべきものと認識し、「JCOG プライバシーポリシー」を定め、万全な管理対策を講じ、プライバシー保護に努める。詳細については、JCOG ホームページ(http://www.JCOG.jp/)参照。

なお、本研究では、患者識別として JCOG0911 の患者登録番号と患者イニシャルのみを使用する。よって、匿名化の作業は行わないものの、個人の特定は出来ず、試料提供者に対する個人情報が流出する危険や不利益は極めて少ない。

7.3.1. JCOG が従うポリシー、法令、規範

JCOG は JCOG 研究を行うにあたり原則として、「JCOG プライバシーポリシー」、の他、以下の法令、規範に従う。下記以外の法令、規範、ポリシーが適応となる場合は、加えて従うこととする。

- 個人情報の保護に関する法律(平成 15 年 5 月 30 日法律第 57 号、最終改正:平成 15 年 7 月 16 日法律第 119 号)
- ヘルシンキ宣言(日本医師会訳)
- 疫学研究に関する倫理指針(平成 14 年 6 月 17 日制定、平成 16 年 12 月 28 日全部改正、平成 17 年 6 月 29 日一部改正、平成 19 年 8 月 16 日全部改正、平成 20 年 12 月 1 日一部改正)

7.3.2. 患者情報の開示等に対する対応

患者本人より JCOG が保有するプライバシーに関する情報の開示などを求められた場合の対応者は、原則として当該患者の医療機関の研究者(施設研究責任者、施設コーディネーター、担当医)とする。

7.3.3. 一般的な問い合わせおよび苦情の受付

プライバシーポリシーに関する一般的な問い合わせや苦情は、下記にて、郵便、電子メール、FAX のいずれかの方法で受け付ける。

問い合わせ窓口: JCOG データセンター プライバシー保護担当
郵送先 :〒104-0045 東京都中央区築地 5-1-1 国立がん研究センター
E-mail :JCOG_privacy@ml.JCOG.jp
FAX :03-3542-3374

7.3.4. プロトコールの遵守

本研究に参加する研究者は、患者の安全と人権を損なわない限り、本プロトコールを遵守する。

7.3.5. 検体・試料の保存、破棄

余剰検体は、JCOG0911 患者登録番号、イニシャルなども削除し全ての試料を破棄する。

7.4. 医療機関の倫理審査委員会の承認

7.4.1. 研究参加開始時の承認

本附随研究への参加に際しては、本プロトコールおよび患者への説明文書を用いて研究を実施することが、各医療機関の承認を得なければならない。

承認が得られた場合、各医療機関の施設コーディネーターは各医療機関の承認文書のコピーを試料解析研究事務局へ送付する(郵送または FAX: 052-744-2361)。承認文書原本は施設コーディネーターが保管、コピーは試料解析研究事務局が保管する。

なお、患者への説明文書は、臨床研究についての諸要件から逸脱しない範囲において医療機関毎に改変を加えたものを当該医療機関の承認を得て用いることができるが、プロトコールについては医療機関毎の内容変更は許容されない。全施設共通のプロトコールを用いる。内容の変更が必要な場合は、全施設で用いるプロトコールとして改正もしくは改訂を行うため、医療機関からプロトコール本文の修正依頼があった場合は、施設コーディネーターは試料解析研究事務局に相談すること。説明文書を医療機関の指示等により改変した場合は、改変した説明文書を試料解析研究事務局に送付する。試料解析研究代表者/試料解析研究事務局は、施設での改変(削除や内容変更)が不適切と判断した場合、施設研究責任者/施設コーディネーターを通じて医療機関に再検討を依頼することができる。

7.4.2. 各医療機関の承認の年次更新

各医療機関における、本プロトコールおよび患者説明文書に対する審査承認の年次更新の要否については各医療機関の規定に従う。審査承認の年次更新が行われた場合であっても、JCOG としては各医療機関の

年次更新承認書の提出は求めない。

7.5. JCOG 研究に関わる者の利益相反(COI)の管理について

JCOG の研究に関わる研究者や JCOG 研究を支援する者の COI は以下のように管理する。

1) 施設研究責任者や施設コーディネーターなど参加施設での診療において JCOG 研究に関わる者の COI については、参加施設の医療機関の規定に従う。
2) 研究代表者や研究事務局、グループ代表者やグループ事務局など、JCOG 研究に中心的な役割をもって関わる者の COI については、JCOG 利益相反委員会が管理する。この他、JCOG の効果・安全性評価委員会などの委員や、個々の JCOG 研究に関わる JCOG データセンター/運営事務局スタッフの COI についても同様に管理する。

8. 研究資金

- 厚生労働科学研究費補助金 がん臨床研究事業(H20-がん臨床-一般-019)

「悪性神経膠腫に対するTemozolomide の治療効果を増強した標準的治療確立に関する研究」班

- 国立がん研究センターがん研究開発費指定研究 20 指-4

「希少悪性腫瘍に対する標準的治療確立のための多施設共同研究」班

9. 予定検体数と研究期間

JCOG0911 の予定登録数が 120 例であることから、本附随研究の登録数は 80-120 例と見込んでいる。いずれかの参加施設において初めて IRB の承認が得られた日をもって研究開始日とし、順次、承認が得られた参加施設からの試料の収集を行う。本体研究(JCOG0911)は 2010 年 4 月より登録が開始され、予定登録期間は 1.5 年、追跡期間は 2 年の総研究期間が 3.5 年の研究である。本附随研究は JCOG0911 の生存期間を用いるため、本附随研究の研究期間は本体研究(JCOG0911)の総研究期間を考慮して 5 年間とする。

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10.5. 参加施設

JCOG0911「初発膠芽腫に対するインターフェロン-β+テモゾロミド併用化学放射線療法のランダム化第 II 相試験」の参加施設のうち、試料の外部提供に関する IRB の承認が得られた施設。

10.6. 統計解析責任者

JCOG データセンター
福田治彦
柴田大朗
水澤純基
試料解析研究事務局
夏目敦至
竹内一郎

11. 委託研究契約

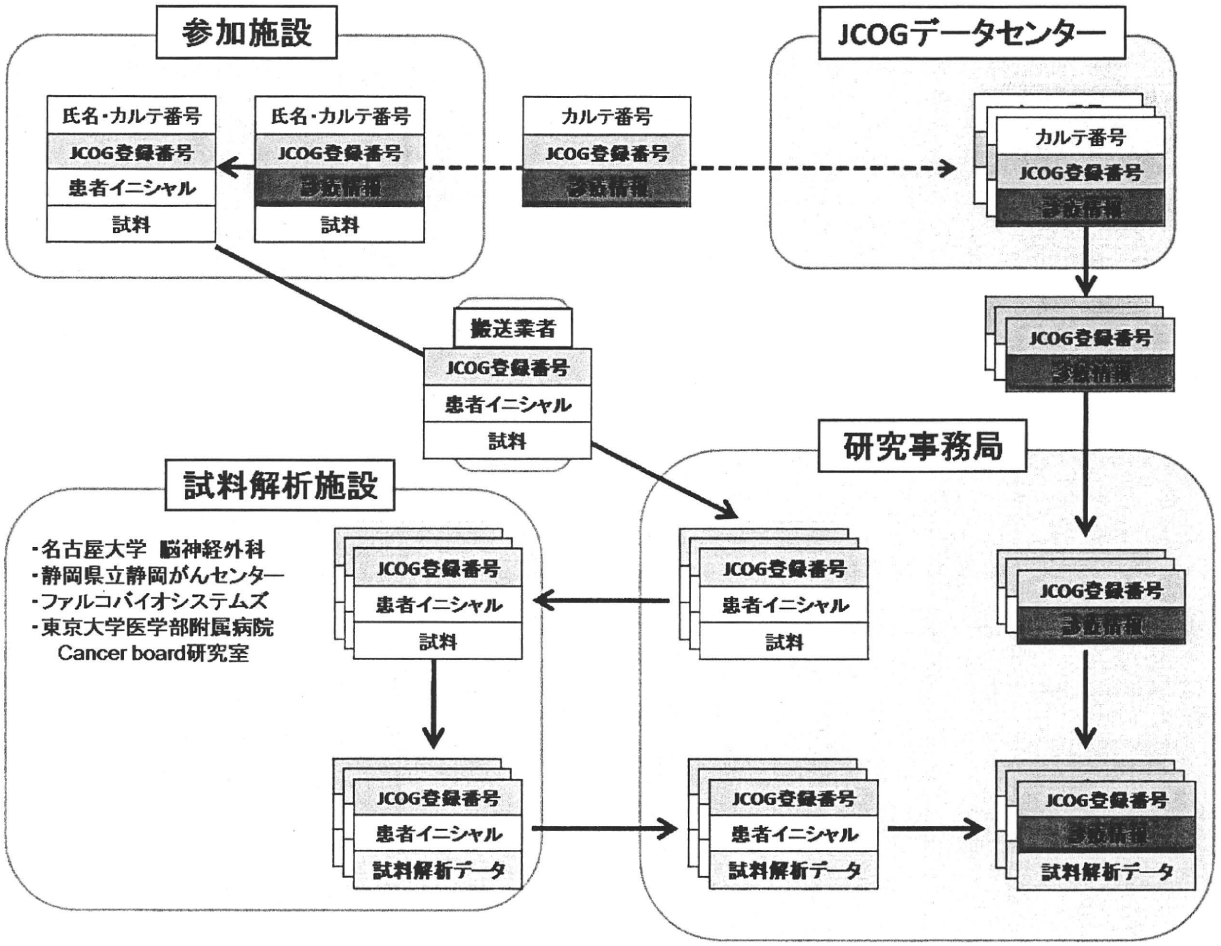
本研究における、Multiplex Ligation-dependent Probe Amplification (MLPA)法に関しては、国立がん研究センターの共同研究に関する規定に従い、株式会社ファルコバイオシステムズと委託研究契約を締結した上で実施する予定である。なお、本研究に要する費用は全て、8.研究資金に記載した通り、厚生労働科学研究費補助金 がん臨床研究事業(H20-がん臨床-一般-019)「悪性神経膠腫に対するTemozolomide の治療効果を増強した標準治療確

立に関する研究」班、および、独立行政法人国立がん研究センターがん研究開発費指定研究 20 指-4「希少悪性腫瘍に対する標準治療確立のための多施設共同研究」班より支出される。

12. 研究結果の公表

共同研究者と協議の上、報告をまとめ公表する。試料解析研究代表者、試料解析研究事務局、共同研究者が共同して論文を作成し、学会発表を行う。

13. 附図:試料の流れ



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in primary glioblastomas (de novo) but not in secondary glioblastomas. J Neuropathol Exp Neurol 1998:57(7):684-689.

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別紙４

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

悪性神経膠腫に対する Temozolomide の治療効果を増強した標準治療確立に関する研究

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研究要旨

希少悪性腫瘍のひとつである悪性神経膠腫の中で、最も予後不良の疾患とされる膠芽腫に対し標準治療となった Temozolomide(TMZ)併用化学放射線療法の治療効果を増強する目的で、Japan Clinical Oncology Group(JCOG)脳腫瘍グループとして、TMZ に Interferon-β（INF-β）を併用する化学放射線療法の有効性を評価するランダム化第 II 相臨床試験を計画し、プロトコールの作成を行い、平成 22 年 4 月より登録を開始した。平成 23 年 3 月末現在 64 例の登録（目標症例数 120）が得られている。

A～H.の報告内容は研究代表者と同一であるため省略する。

研究成果の刊行に関する一覧

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BRIEF REPORT

Acute Lymphoblastic Leukemia After Temozolomide Treatment for Anaplastic Astrocytoma in a Child With a Germline *TP53* Mutation

Hiroyuki Momota, MD,[1,*] Yoshitaka Nariata, MD,[1] Yasuji Miyakita, MD,[1] Ako Hosono, MD,[2] Atsushi Makimoto, MD,[2] and Soichiro Shibui, MD[1]

We present a case of a 12-year-old female with a germline *TP53* mutation who presented with anaplastic astrocytoma and subsequent acute lymphoblastic leukemia (ALL) 13 months after starting treatment with temozolomide (TMZ). The patient had no family history of malignancy except her grand father and his siblings. Although alkylating agents such as TMZ are known to induce secondary hematologic malignancy, only several cases of treatment-related acute leukemia have been reported after TMZ-alone chemotherapy for malignant gliomas. We demonstrate a rare case of TMZ-related ALL in a child with glioma possibly associated with a germline *TP53* mutation. Pediatr Blood Cancer. 2010;55:577–579.

Key words: alkylating agent; glioma; p53; temozolomide; treatment-related acute leukemia

INTRODUCTION

Temozolomide (TMZ) is an oral alkylating agent used in the treatment of gliomas. The main toxicity of TMZ is myelotoxicity [1], but the incidence of grade 3–4 events is less than 10%. Because of its efficacy and tolerability, TMZ has become the first choice of chemotherapy for high-grade gliomas with a prolonged survival [2]. Prior to the introduction of TMZ, alkylating agents such as carmustine (BCNU), lomustine (CCNU), nimustine (ACNU), and procarbazine had been used as a first line for the treatment of malignant gliomas. These alkylating agents and topoisomerase inhibitors (e.g., etoposide) are well known to induce treatment-related myelodysplastic syndrome (t-MDS), acute myeloid leukemia (AML), or acute lymphoblastic leukemia (ALL) in cancer patients [3–5]. The development of t-MDS/AML and ALL are related to dose, therapy duration, and patient age. Since the current TMZ therapy for gliomas has been introduced after the use of other alkylating agents and has shown a prolonged survival, treatment-related acute leukemia (t-AL) may be on the rise in patients with gliomas. However, reports of t-AL associated with TMZ are few and it remains still unclear whether TMZ has the same leukemogenic potential as other alkylating agents. Here, we present a case of ALL occurred in a child with anaplastic astrocytoma after TMZ alone chemotherapy possibly in association with a germline *TP53* mutation.

CASE REPORT

A 12-year-old female developed numbness in her right side and was admitted to another hospital. She had no other medical history, but her grand father had a gastric cancer and he had two siblings with cancer. Magnetic resonance imaging (MRI) of her brain showed bilateral diffuse infiltrating tumors with contrast enhancement. She was transferred to our hospital and underwent biopsy of the right frontal lobe, and diagnosed with anaplastic astrocytoma. She started combination treatment with TMZ and local brain radiotherapy. TMZ was administered orally at 75 mg/m^2/daily for 6 weeks. LBRT was administered simultaneously at whole dose of 60 Gy in 30 fractions of 2 Gy limited in high intensity region of the brain on T2-weighted MRI. After combined therapy, she started maintenance chemotherapy with TMZ at 150 mg/m^2/daily for 5 days. One month later, the dose of TMZ was increased to 200 mg/m^2/daily for 5 days every month and she received 8 more cycles of TMZ. Between fifth and sixth course she developed excessive myelosuppression and chemotherapy was suspended for 2 weeks. Thirty-seven days from the last dose of TMZ, the peripheral blood had 34% leukemic blasts, and the patient was referred to the department of pediatric oncology in our hospital. On admission, the white cell count was 4,100/μl, hemoglobin was 12.3 g/dl, and platelet count was 25,000/μl. The differential count showed 46.0% neutrophils, 4.0% eosinophils, 4.0% monocytes, 11.0% lymphocytes, 3% myelocytes, and 35.0% leukemic blasts. Serum LDH was 663 U/L. A bone marrow aspiration demonstrated a massive infiltration of blast cells (86%). On flow cytometry, the blasts were positive for CD10 (78%), CD19 (100%), HLA-DR (100%), CD45 (100%), TdT (85%), and CD34 (24%). Cytogenetic analysis showed no chromosomal abnormality. A diagnosis of precursor B ALL was made. The patient was treated with induction chemotherapy consisting of prednisolone, vincristine, pirarubicin, and asparaginase. Central nervous system prophylaxis was simultaneously administered with intrathecal methotrexate, cytarabine, and hydrocortisone. Consolidation therapy was started but soon suspended because of complications. Follow-up MRI examinations for brain tumor during the treatment for ALL revealed slight brain atrophy and hydrocephalus without evidence of disease recurrence. She died from pneumonia 8 months after the diagnosis of ALL. We performed DNA sequencing analyses for *TP53* of the tumor and peripheral blood samples collected during the brain biopsy. A premature stop codon (CGA to TGA at codon 213) was detected in both samples, while immunohistochemistry of the p53 protein revealed no positive staining in the tumor tissue.

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Conflict of interest: Nothing to declare.

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TABLE I. Review of the Literature of t-MDS/AML and t-ALL Associated With TMZ-Alone Chemotherapy

Case	Age/ sex	Diagnosis	Radiation (Gy)	Total TMZ dose (mg/m^2)	Latency after TMZ (mo)	Hematological malignancy	Cytogenetics	Refs.
1	40/M	GBM	60.0	3,100	4	ALL	45, XY, −7, der(9) (p12) t(9;22)	[11]
2	44/F	LGA	54.0	24,000	28	MDS	−5, −7	[10]
3	34/F	AOA	59.4	28,000	3	MDS/AML	−5, −7	[10]
4	12/F	AA	60.0	12,900	13	ALL	Normal	Present case

TMZ, temozolomide; GBM, glioblastoma multiforme; LGA, low-grade astrocytoma; AOA, anaplastic oligoastrocytoma; AA, anaplastic astrocytoma; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

DISCUSSION

In this report, we present a case of TMZ-related ALL. The present case is the second published report of treatment-related ALL in glioma patients treated with TMZ and the first published report of t-AL in children after TMZ treatment for gliomas. Since the effect of radiotherapy on secondary MDS/AL is considered to be limited [5], we assume that our case of ALL is mainly related to a treatment with TMZ and a germline *TP53* mutation. Although the reports of t-MDS/AML and ALL in glioma patients treated with nitrosoureas such as BCNU, CCNU, and ACNU have been accumulating [5–7], the leukemogenic activity of another alkylator TMZ has not fully evaluated yet. There are several reports of t-MDS/AML in association with TMZ, however, most of these cases were treated with TMZ after the treatment with other alkylating agents [7–10]. Only four cases of t-MDS/AML and ALL have been reported occurring after chemotherapy with TMZ alone in glioma patients (Table I) [10,11].

Secondary leukemia in cancer survivors accounts for 5–10% of all acute leukemias [12]. Although secondary MDS/AML are the most frequent entities among patients with secondary leukemia, secondary ALL represents certain numbers accounting for about 10% of all secondary leukemia [12,13]. In general, there are other possibilities to explain the development of ALL in cancer patients. One is genetic susceptibility to cancer. Heterozygous *TP53* mutation results in the Li–Fraumeni syndrome of a hereditary predisposition to cancer including astrocytic brain tumor and acute leukemia. However, de novo acute leukemia in patients with the Li–Fraumeni syndrome has been reported to account for only 20 of the 738 cancers (2.7%) in the 185 kindreds [14]; and germ-line *TP53* mutations are uncommon in patients with acute leukemia [15]. Another possibility is that the ALL occurred as a random event. Given the fact that the patient had a *TP53* germline mutation and a family history of cancer in the present case, the genetic background might have a substantial effect on cancer development. Considering of the leukemogenic activity of alkylators and the timing of the onset of ALL, TMZ might also be a primary factor in our patients. Moreover, since TMZ is known to have a toxic effect especially on lymphocytes [16], it is interesting that two out of four TMZ-related MDS/AMLs and ALLs in the reported cases presented as an ALL.

The incidence of treatment-related AL has been reported in a large prospective study of 1,628 brain tumor patients treated with CCNU [6]. In this report, only 10.9% of the study participants were followed for more than two years, and only two cases of treatment-related AL were observed in 1,682 patients (0.12%). As the median latency between the initiation of therapy and the diagnosis of t-MDS/AML and ALL has been reported to be 31 months in brain tumor patients and to be 50–70 months in patients with other malignancies [5,17,18], the incidence of treatment-related AL may be much higher than those reported. Chamberlain and Raizer [10] have reported seven cases of t-MDS/AML during the treatment of gliomas. Of the seven patients, five patients had been treated with nitrosoureas and TMZ, and two patients with TMZ alone. These data indicate that the combination of nitrosourea and TMZ may increase the incidence of alkylator-induced MDS/AML and ALL. However, there are no data to suggest that TMZ is more likely to induce secondary hematological malignancies than nitrosoureas or to enhance the leukemogenic activity of other alkylators.

In conclusion, increasing evidence indicate that TMZ may have the same leukemogenic potential as other alkylating agents. As TMZ has only been approved in the last decade and the survival rate in glioma patients has increased, TMZ-related MDS/AML and ALL will become more frequent. Although treatment-related ALL is a relatively rare entity in secondary leukemia, it may become more problematic in patients with glioma because of the increased use of TMZ.

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