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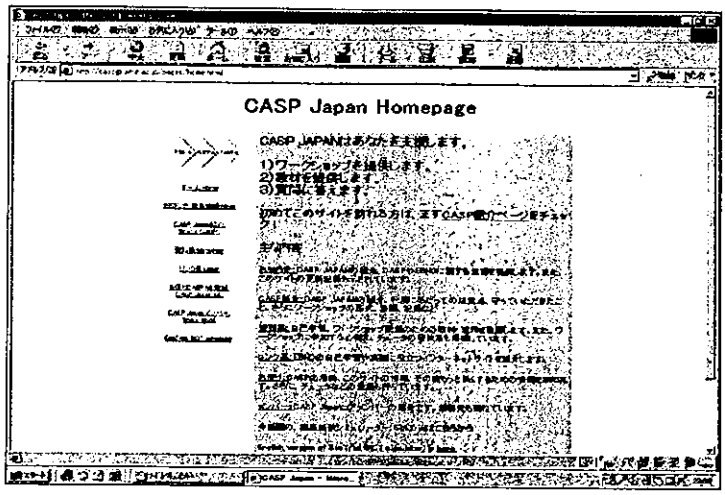

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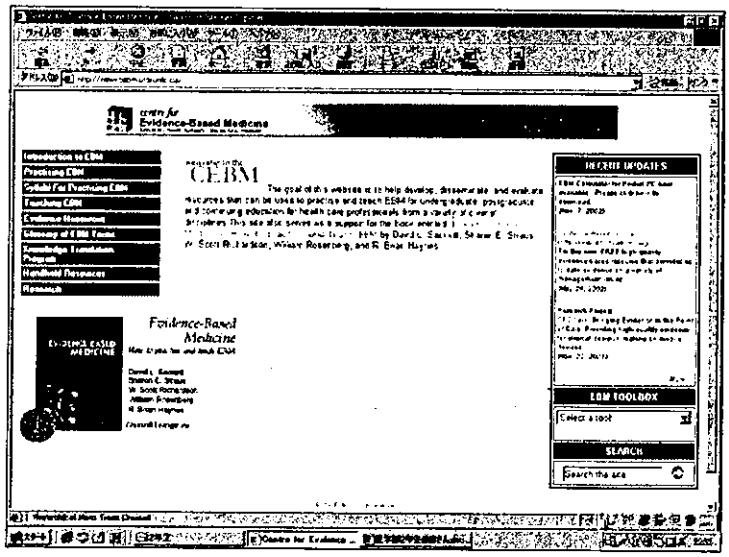

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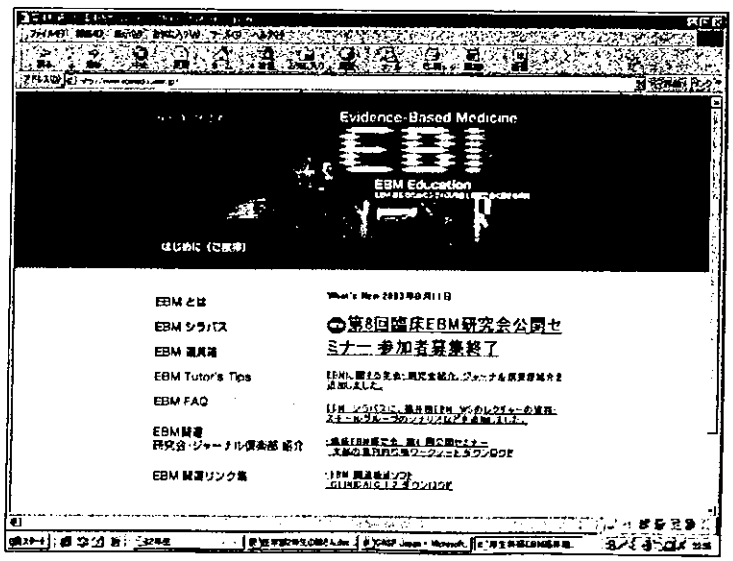

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内容の検討:
目を通すことのできる数まで絞り込んだ後に，一つ一つの文献をタイトルや抄録を読んで必要な文献を取り寄せる．忙しい診療の合間に文献を読むことになるので，できる限り必要な文献のみに絞ることが大事である．

【治療のシナリオ】

あなたは鍋島総合病院の1年目の研修医である。救急外来から入院した70歳男性の脳梗塞患者の担当になった。ひととおり診察を終え、検査データの確認も済み、指導医と治療について相談した。

指導医：「ひととおり終えたところで、治療はどうする。」
研修医：「はい、意識も比較的保たれていて、診察とCTなどの結果から中大脳動脈領域の脳梗塞です。既往歴は高血圧だけで、不整脈や心疾患の病歴もなく、アテローム血栓性脳梗塞だと思います。治療は、維持輸液とグリセオールを開始しました。」
指導医：「そうだね。この間、医師会主催の講演会を聞きに行ったら、エダロボンという脳保護薬はどのようなタイプの脳梗塞にも使えていいみたいだから、ちょっと使ってみようか。」
研修医：「は、はい。それ聞いたことがあります。でも、先生、明日の○○先生の回診では、新しい薬を使うと必ずエビデンスはあるのかって聞かれますよ。いいエビデンスがあるのですか。」
指導医：「なかなかいいところをつくね。明日までに時間があるから、ちょっとMedlineで検索して、図書館からいい文献を見つけてきてくれないか。」
研修医：「は、は、はい。（ああ、今日のデートもキャンセルか、あとで携帯にメールしておかない。はあー）」
指導医：「今日は当直だし、学会の準備もあるからずっと起きているよ。いつでもいいから連絡してね。時間があればいっしょに文献を読もうか。」
研修医：「は、はい、わかりました。お願いします。」

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Effect of a Novel Free Radical Scavenger, Edaravone (MCI-186), on Acute Brain Infarction

Randomized, Placebo-Controlled, Double-Blind Study at Multicenters

The Edaravone Acute Brain Infarction Study Group (Chair: Eiichi Otomo, MD)[1]

Key Words
Clinical trial · Free radical · Neuroprotection · Acute stroke

Abstract
Edaravone, a novel free radical scavenger, demonstrates neuroprotective effects by inhibiting vascular endothelial cell injury and ameliorating neuronal damage in ischemic brain models. The present study was undertaken to verify its therapeutic efficacy following acute ischemic stroke. We performed a multicenter, randomized, placebo-controlled, double-blind study on acute ischemic stroke patients commencing within 72 h of onset. Edaravone was infused at a dose of 30 mg, twice a day, for 14 days. At discharge within 3 months or at 3 months after onset, the functional outcome was evaluated using the modified Rankin Scale. Two hundred and fifty-two patients were initially enrolled. Of these, 125 were allocated to the edaravone group and 125 to the placebo group for analysis. Two patients were excluded because of subarachnoid hemorrhage and disseminated intravascular coagulation. A significant improvement in functional outcome was observed in the edaravone group as evaluated by the modified Rankin Scale ($p = 0.0382$). Edaravone represents a neuroprotective agent which is potentially useful for treating acute ischemic stroke, since it can exert significant effects on functional outcome as compared with placebo.

Introduction

Data have been accumulated which demonstrate that free radicals play a crucial role in brain injury following ischemia [1–3]. In the ischemic state, the metabolism of arachidonic acid is accelerated within the brain tissue [4, 5], including the brain microvessels [6], leading to an increase in free radical production. Free radicals cause membrane injury through peroxidation of unsaturated fatty acids in the phospholipids constituting the cell membrane, and such injury progresses sequentially, leading to ischemic brain injury as represented by neuronal death and brain edema [7].

A novel free radical scavenger, edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one, MW: 174.20), has been shown to inhibit lipid peroxidation [8] and vascular endothelial cell injury [9] in vitro. In rat brain ischemic models, edaravone can ameliorate brain edema [10, 11],

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Table 1. The grade of neurological deficits

Neurological deficit	Categories					
	0	1	2	3	4	5
Aphasia	normal	no problems in daily conversation, but aphasic symptoms present	slight disturbance in daily conversation	difficulty to understand, but possible	almost impossible to understand	
Dysarthria	normal	very slight	slurs in at least some words, but could be understood with some difficulty	moderate	unable to be understood	
Dysphagia	normal	very slight	choking occasionally	unable to swallow occasionally with difficulty	unable to swallow	
Sensory disturbance	normal	very slight	tolerable sensory paralysis and/or abnormal sensation	moderate	loss of sensation and/or intolerable abnormal sensation	
Muscle strength of the legs and arms with motor weakness	normal	able to move .. against resistance	able to move against gravity	able to move when gravity was removed	presence of muscle contraction	absence of muscle contraction

tissue injury [8, 12, 13], delayed neuronal death [14] and neurological deficits [11, 12]. Additionally, it can prevent cerebral vasospasm in canine subarachnoid hemorrhage models [15].

Edaravone was therefore expected to have a neuroprotective effect in cases of acute brain infarction. It was first evaluated in an early phase 2 study [16] at doses of 20, 30 and 60 mg, twice a day, in 85 patients with acute brain infarction, and subsequently in a late phase 2 double-blind study [17] at doses of 10, 30 and 45 mg, twice a day, in 356 patients within 72 h of onset. The results of these clinical studies demonstrated improvement in neurological deficits without serious safety problems. On the basis of the above investigations, the appropriate dosage was considered to be 30 mg (i.v., b.i.d.) for 14 days.

The present multicenter, randomized, placebo-controlled double-blind study was carried out in order to verify the efficacy of edaravone (30 mg, i.v., b.i.d.) in terms of functional outcome in patients with acute ischemic stroke.

Materials and Methods

Patients

The study was conducted at institutions throughout Japan from December 1993 through March 1996 (see Appendix).

The criteria for inclusion were as follows: (1) inpatients within 72 h after the onset of ischemic stroke including patients that were both thrombotic and embolic in nature, and (2) patients with a level of consciousness between 0 (alert) and 30 (able to be aroused with mechanical or verbal stimuli) according to the Japan Coma Scale [18]. Patients who could not be aroused with forceful mechanical stimuli (levels 100–300) were excluded.

Prior to enrollment in the study, informed consent was obtained from each patient or the patient's next-of-kin, if the patient was not competent to take this responsibility. The protocol and consent form employed during the trial were approved by each participating center's institutional review board. The study was performed in accordance with Good Clinical Practice (Ministry of Health and Welfare of Japan).

Test Drugs and Random Allocation

The active drug was provided in 20-ml ampoules containing 30 mg of edaravone. Physiological saline, indistinguishable from the active drug, was used as the placebo. Mitsubishi Pharma Corporation supplied the test drugs. The controller, who randomly allocated the test drugs, confirmed the indistinguishability.

Dosage and Administration

One ampoule was diluted in 100 ml of physiological saline and administered by intravenous drip infusion over a period of 30 min, every 12 h for 14 days. Intravenous infusion of 400–600 ml of 10% glycerol was allowed to give if needed. The use of fibrinolytic agents (urokinase and recombinant tissue plasminogen activator), citicoline, and ozagrel sodium was avoided throughout the study period.

Observation Parameters

The patient characteristics, including sex, age, stroke subtype, time to treatment after onset, level of consciousness according to the Japan Coma Scale, neurological deficits evaluated according to table 1, associated diseases, and CT or MRI findings, were recorded. Thrombotic and embolic infarctions were diagnosed according to the

Table 2. Baseline characteristics

Characteristics	Edaravone (n = 125)	Placebo (n = 125)	Statistics[4]
Sex (M/F)	82/43	84/41	χ^2: p = 0.893
Age, years			
≤65/65<	42/83	48/77	χ^2: p = 0.510
Mean ± SD	66.3 ± 8.0	66.1 ± 8.5	t: p = 0.836
Stroke subtype			
Thrombotic	97	101	χ^2: p = 0.809
Embolic	24	21	
Not determined	4	3	
Time to treatment after stroke onset, h			
≤24	42	39	χ^2: p = 0.218
25–48	41	56	
48<	42	30	
Mean ± SD	37.3 ± 22.6	35.2 ± 26.6	t: p = 0.488
Level of consciousness before treatment[1]			
Alert (0)	79	81	χ^2: p = 0.132
Grade I (1, 2, 3)[2]	37	27	
Grade II (10, 20, 30)[3]	9	17	
Aggregate score for neurological deficits before treatment			
Median (Q1, Q3)	6 (4, 11)	6 (4, 10)	W: p = 0.628
Associated diseases			
Hypertension	75	72	
Diabetes mellitus	26	29	
CT or MRI findings before treatment			
Infarction (+/–)	94/31	86/39	χ^2: p = 0.324
Middle cerebral artery/others	75/19	67/19	χ^2: p = 0.900
Perforator/cortex	57/37	56/29 (not determined: 1)	χ^2: p = 0.568
Use of 10% glycerol	111	111	χ^2: p = 1.000

[1] Japan Coma Scale.
[2] Grade I: patient is awake without any stimuli, and is: (1) almost fully conscious; (2) unable to recognize time, place, and person; (3) unable to recall name or date of birth.
[3] Grade II: patient can be aroused (then reverts to previous state after cessation of stimulation): (10) easily by being spoken to (or is responsive with purposeful movements, phrases, or words); (20) with loud voice or shaking of shoulders (or is almost always responsive to very simple words like 'yes' or 'no', or to movements); (30) only by repeated mechanical stimuli.
[4] χ^2 = chi-square test; t = t test; W = Wilcoxon's rank sum test.

criteria proposed by Minematsu et al. [19], in which the mode of onset, presence or absence of underlying heart diseases and other factors were included.

The outcome was assessed according to the modified Rankin Scale [20] at discharge within 3 months or at 3 months after onset. Additionally, we collected outcome data at 3, 6 and 12 months after onset.

Physical examinations and routine clinical laboratory tests (hematology, blood chemistry and urinalysis) were performed before the treatment and on days 7 and 14 of the treatment.

Handling of the Patients' Data

The handling of patients with incomplete data was discussed by the Steering Committee (see Appendix) before the key break. The data were frozen, until the key codes were broken, and the data analysis was then performed subsequently. The data were subjected to intent-to-treat analysis.

Statistical Analysis

Comparisons of the modified Rankin Scale were undertaken by Wilcoxon's rank sum test, with the criterion for significance set at 5% (two-tailed).

Table 3. Functional outcome assessed at discharge within 3 months or at 3 months after onset, using the modified Rankin Scale

Functional outcome	Edaravone (n = 125)	Placebo (n = 125)
0 No symptoms at all	27	12
1 No significant disability despite symptoms	36	35
2 Slight disability	29	40
3 Moderate disability	12	12
4 Moderately severe disability	10	15
5 Severe disability	7	6
Death	4	5
Wilcoxon's rank sum test	p = 0.0382	

Table 4. Modified Rankin Scale assessed at 3 months, 6 months and 12 months after onset

Grade	3 Months		6 Months		12 Months	
	edaravone (n = 115)	placebo (n = 113)	edaravone (n = 105)	placebo (n = 103)	edaravone (n = 100)	placebo (n = 94)
0	26	10	27	9	27	8
1	34	39	35	37	31	35
2	24	26	15	23	14	19
3	10	11	11	10	8	7
4	9	14	3	9	4	11
5	7	7	8	7	6	5
Death	5	6	6	8	10	9
p[1]	0.0481		0.0112		0.0248	

[1] Wilcoxon's rank sum test.

Results

A total of 252 patients were registered; of whom 125 were assigned to the edaravone group and 127 were assigned to the placebo group. Among them, 1 patient in the placebo group who had suffered subarachnoid hemorrhage and 1 patient in the placebo group who turned out to have disseminated intravascular coagulation (DIC) due to ovarian tumors immediately after the start of treatment and subsequently died as a result of brain hernia following hemorrhagic infarction were excluded from the analysis. Thus, 250 patients, comprising 125 in the edaravone group and 125 in the placebo group, were eligible for intent-to-treat analysis.

The patient characteristics of the two groups were comparable as shown in table 2. There was no difference between both groups.

Efficacy

Table 3 lists the results for the analysis using the modified Rankin Scale performed at discharge within 3 months or at 3 months after onset. There was a significant difference (p = 0.0382, Wilcoxon's rank sum test) between the groups in favor of the edaravone group. The average time from onset to assessment was 49 days in the edaravone group and 50 days in the placebo group. Additionally, based on the outcome data at 3, 6 and 12 months after onset, the above benefit was sustained for relatively longer as shown in table 4. When subset analysis was undertaken for the patients treated within 24 h, the difference between the two groups was clearer than that in the whole patient analysis, as shown in table 5.

Safety

Adverse reactions were observed in 9 patients (7%) in the edaravone group and in 14 patients (11%) in the pla-

Table 5. Modified Rankin Scale assessed at discharge within 3 months or at 3 months after onset, in patients treated within 24 h after onset

Grade	Edaravone (n = 42)	Placebo (n = 39)
0	14	1
1	10	6
2	8	13
3	5	3
4	2	8
5	2	4
Death	1	4
	p = 0.0001[a]	

[a] Wilcoxon's rank sum test.

cebo group. Such reactions in the edaravone group consisted of skin rash in 4 patients, abnormal liver function in 3, itching and nausea in 1, and fever and abnormal liver function in 1, but recovery was achieved during or after the treatment. In the placebo group, the adverse reactions that occurred included skin rash in 2 patients, abnormal liver function in 6, diarrhea, fever and acute renal failure in 1, a bleeding tendency and DIC in 1, increases in white blood cell, lactate dehydrogenase and serum amylase in 1, epigastric discomfort in 1, anxiety attack and dyspnea in 1, and anemia and abnormal liver function in 1. Abnormal changes in laboratory tests were observed mainly to involve parameters of the liver functions (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase), and the proportions of patients with such changes amounted to about 10% in each group.

Four patients in the edaravone group and 5 patients in the placebo group died. The causes of death in the edaravone group were exacerbation of brain infarction, sudden cardiac arrest, pneumonia, and suicide due to mental depression in 1 patient each, and the relation to the test drug was judged to be nil. In the placebo group, the causes of death comprised exacerbation of brain infarction in 1 patient, advanced brain edema or tonsillar herniation in 2, pneumonia in 1, and DIC assumed to be due to large infarct and liver cirrhosis in 1.

Discussion

Neuroprotective drugs are expected to extend the therapeutic time window after stroke with fibrinolytic therapy by inhibiting cell death and blocking reperfusion injury, and a combination of both drugs could provide new weapons for effective treatment of stroke in the future [21]. Several studies have indicated the presence of an area of constrained blood flow with partially preserved energy metabolism, the so-called ischemic penumbra, around the ischemic core within the brain of animal models as well as stroke patients, allowing drugs to reach and prevent the progress to infarct in this area [22–24]. Drug treatments for acute ischemic stroke can be roughly divided into antithrombotic agents, such as thrombolytics, anticoagulants and antiplatelets, and neuroprotective agents, such as free radical scavengers.

Edaravone has been reported to inhibit vascular endothelial cell injury [9], brain edema [10, 11], tissue injury [8, 12, 13] and delayed neuronal death [14], and consequently lessens neurological deficits [11, 12]. Additionally, preservation of N-acetyl-aspartate, a neuron-specific amino acid, in the ischemic brain of edaravone-treated patients as revealed by sequential MR spectroscopic examinations has been reported [25]. In terms of its chemical characteristics, edaravone can inhibit peroxidation of the phosphatidylcholine liposomal membrane initiated by water-soluble as well as lipid-soluble radicals, which makes it comparable to ascorbic acid and α-tocopherol, which are well-known antioxidants [26]. Contrary to superoxide dismutase, another free radical scavenger, which has difficulty in penetrating the blood-brain barrier (BBB), edaravone is a low-molecular-weight radical scavenger, of which the BBB permeability has been estimated to be around 60% [27], eliminating highly cytotoxic hydroxyl radicals in the brain following intravenous administration [14]. In fact, edaravone can diminish increases in the levels of hydroxyl radicals after infusion which appear to be preferentially produced in the perifocal ischemic area, possibly the ischemic penumbra, resulting in reducing the extent of brain damage [13]. Edaravone does not affect blood coagulation, platelet aggregation, fibrinolysis or bleeding time [28, 29], so that there is no additional risk of bleeding. Edaravone is therefore regarded as a readily utilizable neuroprotective drug with a free radical scavenging action. The effective concentration of this drug in in vitro experiments was found to be 10^{-6}–10^{-5} mol/l, and the plasma concentration at an effective dose in animal experiments was 988–1,729 ng/ml (5.7–9.9 × 10^{-6} mol/l) [30]. The pharmacokinetics

have been investigated in healthy volunteers, and the C_{max} and AUC were found to increase in proportion to the dose [31]. Further, the plasma concentration of the drug when administered to the elderly at the same dose as that employed in the present study was reported to be 1,041 ng/ml (6×10^{-6} mol/l) [32]. The effective concentration in nonclinical studies and the plasma concentration encountered in actual clinical practice agree well.

As regards the time to treatment after the onset of stroke, we set the inclusion criterion as within 72 h, since the time did not appear to influence the efficacy so much in the late phase 2 study [17]. In general, the duration of brain edema in humans is several times longer than that in the rat which shows a tendency to decrease after 3 days of infarction [33]. Recently, Matsui et al. [34] indicated that the infarct volume slowly increased from 24 h until as late as 168 h after permanent focal ischemia in rats, and Peters et al. [35] suggested prolonged oxidative stress after cerebral infarct, which can trigger intraparenchymal neutrophil infiltration leading to oxidative damages of BBB and neuronal cells persisting for at least 5 days or longer in patients [36].

The data obtained in the present study demonstrated that the effects of edaravone on the functional outcome were significantly superior to those of the placebo. During 12 months of follow-up, the outcome data indicated a sustained benefit for edaravone in acute ischemic stroke patients. As regards the time to treatment after stroke onset, the results for the patients treated within 24 h were clearer than those for the patients treated within 72 h after onset.

The major adverse reactions were skin rash and abnormal liver function, but their incidence did not differ significantly between the groups, or was rather more frequent in the placebo group when considering other adverse reactions. There were thus no serious problems in terms of safety.

These findings suggest that edaravone exerts a neuroprotective effect in humans, and has a promising potential for clinical use. Besides the neuroprotective action evident in the single treatment described above, edaravone, due to the absence of a bleeding risk, can also be expected to offer future advantages in combination therapy with fibrinolytic agents and antithrombotics by scavenging the free radicals associated with reperfusion injury, leading to an expansion of the therapeutic time window. We therefore conclude that edaravone represents a promising neuroprotective agent in the treatment of acute ischemic stroke.

Appendix

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Participating Centers

Neurosurgery, Hokkaido University; Neurology, Hokkaido University; Neurosurgery, Hokkaido Neurosurgical Memorial Hospital; Neurosurgery, Nakamura Memorial Hospital; Neurosurgery, Kashiwaba Neurosurgical Hospital; Internal Medicine, Jikeikai Hospital; Neurology, Bibai Rosai Hospital; Neurosurgery, Hakodate Red Cross Hospital; Neurology, Research Institute for Brain and Blood Vessels-Akita; Neurology, Iwate Medical University; Neurology, Iwate Prefectural Central Hospital; Neurology, Tohoku University; Neurology, Kohnan Hospital; Internal Medicine, Saito Hospital; Neurology, Miyagi National Hospital; Neurosurgery, Aizu Central Hospital; Neurological Institute, Ohta Atami Hospital; Neurology, Niigata University; Neurology, Niigata Citizens Hospital; Neurology, Geriatric Institute Hospital; Internal Medicine, Tochigi Kennan General Hospital; Neurology, Saiseikai Utsunomiya Hospital; Internal Medicine, Ohtawara Red Cross Hospital; Neurology, Ashikaga Red Cross Hospital; Internal Medicine, Tajirigaoka Hospital; Neurosurgery, Saitama Medical Center School; Neurology, Urawa City Hospital; Neurosurgery, Kameda General Hospital; Neurosurgery, Tokyo University; Neurology, Tokyo University; Internal Medicine, Nippon Medical School; Neurology, Keio University; Neurosurgery, Tokyo Women's Medical College; Neurology, Tokyo Women's Medical College; Internal Medicine, Tokyo Women's Medical College 2nd Hospital; Neurosurgery, Tokyo Metropolitan Bokutou Hospital; Internal Medicine, Tokyo Saiseikai Central Hospital; Neurosurgery, Keiai Hospital; Internal Medicine, Kosei Hospital; Internal Medicine, Yokufukai Geriatric Hospital; Neurosurgery, Kyorin University; Neurology, Showa General Hospital; Neurology, Tokyo Metropolitan Tama Geriatric Medical Center; Internal Medicine, Kawasaki City Kawasaki Hospital; Neurology, Kawasaki City Ida Hospital; Neurology, Showa University Fujigaoka Hospital; Internal Medicine, Kitasato University; Neurology, Tokai University; Internal Medicine, Tokai University Oiso Hospital; Internal Medicine, Odawara City Hospital; Neurosurgery, Fuji Brain Institute Hospital; Neurology, Shimizu City Hospital; Neurology, East Nagoya National Hospital; Internal Medicine, Nagoya National Hospital; Neurology, Nagoya 1st Red Cross Hospital; Neurology, Nagoya 2nd Red Cross

Hospital; Neurology, Nagoya Ekisaikai Hospital; Neurology, Chukyo Hospital; Neurology, Chubu Rosai Hospital; Neurology, Fujita Health University; Neurology, Tosei General Hospital; Neurology, Gifu Prefectural Tajimi Hospital; Neurology, Toki City General Hospital; Neurology, Mie University; Neurology, Matsusaka Central General Hospital; Neurology, Kanazawa Medical College; Neurosurgery, Shiga Medical Center for Adult Disease; Neurosurgery, Kyoto University; Internal Medicine, Kyoto Prefectural University of Medicine; Neurology, Kyoto Prefectural University of Medicine; Neurosurgery, Shimizu Hospital; Internal Medicine, Osaka University; Neurology, Osaka University; Internal Medicine, National Cardiovascular Center, Cerebrovascular Division, Department of Medicine, National Cardiovascular Center; Neurosurgery, Osaka Red Cross Hospital; Neurosurgery, Tominaga Neurosurgical Hospital; Internal Medicine, Osaka National Hospital; Internal Medicine, Osaka Rosai Hospital; Department of Cerebrovascular Disease, Yodogawa Christian Hospital; Neurology, Kitano Hospital; Internal Medicine, Kobe Ekisaikai Hospital; Neurosurgery, Okayama University; Neurosurgery, Kosei Hospital; Neurosurgery, Kajikawa Hospital; Neurosurgery, Tottori University; Neurology, Tottori University; Neurosurgery, Nojima Hospital; Internal Medicine, Shimane Medical University; Internal Medicine, Tsuwano Kyozon Hospital; Internal Medicine, Nichihara Kyozon Hospital; Neurology, Yamaguchi University; Neurology, Syutou General Hospital; Neurosurgery, Tokushima University; Neurosurgery, Taoka Hospital; Neurology, Kyushu Rosai Hospital; Stroke Unit, Kyushu Rosai Hospital; Neurosurgery, Kita-Kyushu City Yahata Hospital; Internal Medicine, Kyushu University; Internal Medicine, Yagi Hospital; Internal Medicine, Kurume University; Department of Cerebrovascular Disease, St. Maria Hospital; Internal Medicine, Ohmuta Rosai Hospital; Internal Medicine, Fukuoka-East National Hospital; Neurosurgery, Sasebo City General Hospital; Neurosurgery, Nagasaki University; Internal Medicine, Kagoshima University; Neurology, Kikuno Hospital.

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Evidence Based Medicine ワークシート1

EBM ワークショップ資料

学習者氏名________________

記入日時 ________________

患者の問題（簡単な患者紹介と疑問点）:

____

____

____

____

問題の定式化（Step1）:

1. （P）患者 ________________

2. （E）介入 ________________

3. （C）介入の比較 ________________

4. （O）結果 ________________

問題の領域:

（診断、治療、予後、副作用、因果関係、予防、その他）

必要な情報の種類（研究デザイン）:

（ランダム化比較試験、コホート研究、症例対照研究、検査の感度と特異度、
検査の危険性、症例集積報告、症例報告、総説、決断分析、メタ分析、ガイドライン、
医療経済学的分析）

Evidence Based Medicine ワークシート 2

検索前の自分の考え：

情報源：

（マニュアル、教科書、Medline、EBM、ACP journal club、Cochrane Library、
その他（ 専門家に聞く））

検索方法（Step2）：

参考文献：（研究デザイン；＿＿＿＿＿＿＿＿＿＿ ）

Evidence Based Medicine ワークシート3

エビデンスの質の評価 Critical Appraisal (Step3) :

文献：

P：

E：

C：

O：

治療について

I この治療の試験の結果は妥当か？

A.

1．患者の治療への割り付けは無作為か？ Yes No

2．Intent-to-treat 解析か？ Yes No

B.

1．Double blind か？ Yes No

2．実験的治療以外は、いずれの群も同じように治療されたか？

Yes No

3．試験開始時に、いずれの群も類似していたか？

Yes No

II.この無作為化試験の妥当な結果は重要か？

III 自分の患者の医療に適応できるか？

1．自分たちの患者群と似ているか？

2．療計画とその結果は、自分の患者の価値観や選好を満足させるか？

患者への適応（Step4）：

今回の EBM 実践の自己評価（Step5）：

（ワークショップ演習用）
Evidence Based Medicine ワークシート

EBM ワークショップ資料

学習者氏名＿＿山城清二＿＿＿＿＿＿＿＿
記入日時 ＿＿Nov. 28. 2004＿＿＿＿＿＿＿

患者の問題（簡単な患者紹介と疑問点）：

最近、エダラボン（ラジカット）の使用頻度が高い。本当にＭＲさんが言うようにエビデンスがあるのか。EBM の Step に沿って調べてみる。

問題の定式化（Step1）：

1．(P)患者	脳梗塞の患者（subtype は問わず）
2．(E)介入	エダラボン使用あり
3．(C)介入の比較	エダラボン使用なし
4．(O)結果	神経障害の改善

問題の領域：

（診断、治療、予後、副作用、因果関係、予防、その他）

必要な情報の種類（研究デザイン）：

（ランダム化比較試験、コホート研究、症例対照研究、検査の感度と特異度、
検査の危険性、症例集積報告、症例報告、総説、決断分析、メタ分析、ガイドライン、
医療経済学的分析）

Evidence Based Medicine ワークシート2

検索前の自分の考え：

エダラボンはどのタイプの脳梗塞にも使用できると言われているが、本当にエビデンスはあるのか。世界に通用するのか？日本の文献しかないと思われるが、とにかく調べてみようか。

情報源：

（マニュアル、教科書、Medline、EBM、ACP journal club、Cochrane Library、その他(専門家に聞く))

検索方法（Step2）：

#	Search History	Results	Display
1	edaravone.mp.	12	Display
2	from 1 keep 2	1	Display

参考文献：(研究デザイン；　ランダム化比較試験　)

1. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Cerebrovascular Diseases. 15(3):222-9, 2003.*
UI: 12715790

Evidence Based Medicine ワークシート 3

エビデンスの質の評価 Critical Appraisal (Step3) :

文献：Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters

P : _____

E : _____

C : _____

O : _____

治療について

I この治療の試験の結果は妥当か？

A.

1．患者の治療への割り付けは無作為か？ Yes No

2．Intent-to-treat 解析か？ Yes No

B.

1．Double blind か？ Yes No

2．実験的治療以外は、いずれの群も同じように治療されたか？

Yes No

3．試験開始時に、いずれの群も類似していたか？

Yes No

_____

_____

II.この無作為化試験の妥当な結果は重要か？

_____

_____

_____

_____

_____

_____

_____

_____

III 自分の患者の医療に適応できるか？

1．自分たちの患者群と似ているか？

2．療計画とその結果は、自分の患者の価値観や選好を満足させるか？

患者への適応（Step4）：

今回の EBM 実践の自己評価（Step5）：

Evidence Based Medicine ワークシート3

エビデンスの質の評価 Critical Appraisal (Step3)：

文献：Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters

P：72時間以内に発症した脳梗塞の患者、平均年齢66歳、男女比なし。

E：エダラボン30mg, 1日2回、14日間

C：エダラボンなし

O：functional outcome　の変化

治療について

I この治療の試験の結果は妥当か？

A.

1．患者の治療への割り付けは無作為か？　Yes。

2．Intent-to-treat解析か？　Yes。

B.

1．Double blindか？　Yes。

2．実験的治療以外は、いずれの群も同じように治療されたか？　Yes。

3．試験開始時に、いずれの群も類似していたか？　Yes。

Table2に示しているが、性、年齢、stroke subtype、発症からの時間、治療前の意識状態、神経障害の程度、関連疾患（高血圧、糖尿病）の有無、CTとMRIの所見では統計的に有意差はない。

II.この無作為化試験の妥当な結果は重要か？

Table 3. Functional outcome assessed at discharge within 3 months or at 3 months after onset, using the modified Rankin Scale

Functional outcome	Edaravone (n = 125)	Placebo (n = 125)
0 No symptoms at all	27	12
1 No significant disability despite symptoms	36	35
2 Slight disability	29	40
3 Moderate disability	12	12
4 Moderately severe disability	10	15
5 Severe disability	7	6
Death	4	5
Wilcoxon's rank sum test	p = 0.0382	