Intracerebral haemorrhage during alemtuzumab administration

Alemtuzumab is a monoclonal antibody that targets CD52, a protein expressed at high levels on T and B lymphocytes, and at lower levels on other components of the innate immune system.[1] Alemtuzumab 12 mg per day is administered intravenously over five consecutive days, followed by a second course on three consecutive days 12 months later.[1] Alemtuzumab is a potent disease-modifying therapy for the treatment of relapsing-remitting multiple sclerosis,[2–4] with efficacy sustained over several years, even in the absence of continued treatment.[5,6] However, despite its efficacy, use of alemtuzumab has been restricted by serious and potentially fatal risks,[1–4,7] and intense monitoring is required during alemtuzumab administration. Infusion reactions, probably related to cytokine release syndrome, occur in more than 90% of patients.[1–4]

Intracranial haemorrhage can be a remote complication of alemtuzumab therapy. One intracranial haemorrhage case occurred during a phase 2 trial[2] in a patient with relapsing-remitting multiple sclerosis and immune thrombocytopenia 19 months after initial alemtuzumab administration, and a second fatal case was reported[8] in a patient with relapsing-remitting multiple sclerosis 27 months after alemtuzumab administration. On Nov 29, 2018, the US Food and Drug Administration released a safety communication regarding 13 cases of ischaemic or haemorrhagic stroke and cervical arterial dissection associated with alemtuzumab treatment,[9] 12 of which occurred within one day of initiating treatment. We have retrospectively identified five cases of spontaneous intracranial haemorrhage that occurred during the initial 5-day course of alemtuzumab administration, in four US multiple sclerosis centres, between March, 2016, and October, 2017.

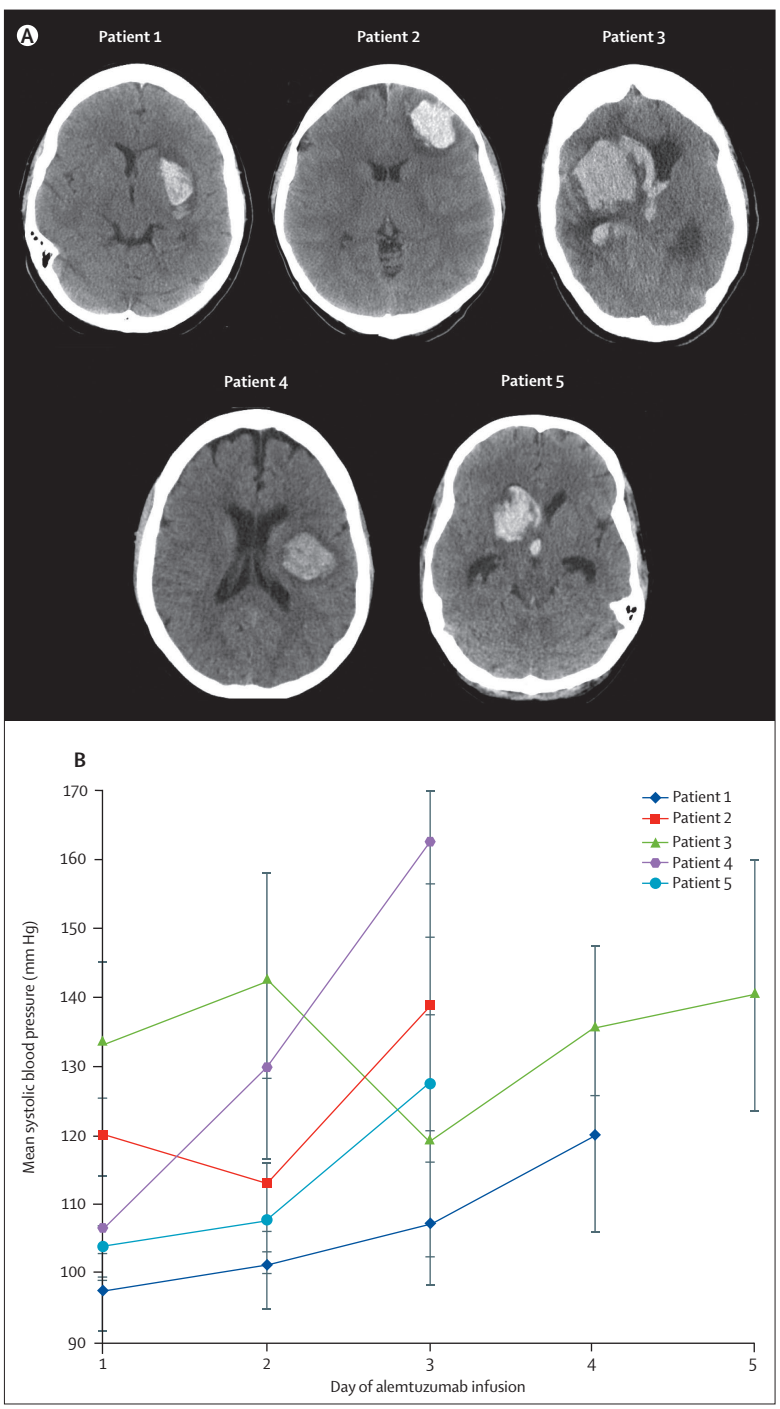

Figure: **Intracerebral haemorrhage and daily mean systolic blood pressures during alemtuzumab administration**
Representative CT scans from each of our five patients demonstrating acute intracerebral haemorrhage (A) and daily mean systolic blood pressure in these patients during the course of alemtuzumab administration (B). Bars represent SD.

All five patients were women (aged 38–49 years), had relapsing-remitting multiple sclerosis with long disease

Published Online
February 15, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30076-6

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on July 8, 2019

durations (8–21 years), had been exposed to two or more treatments before alemtuzumab, and met 2010 McDonald Criteria.[10] We collected detailed information on medical history, concomitant medications, infusion courses and protocols, blood pressure, and intracranial haemorrhage characteristics (appendix). Our patients did not have a history of bleeding disorder; stroke; intracranial haemorrhage; aneurysm; hypertension; connective-tissue or rheumatological disease; or concomitant use of antihypertensives, anticoagulants, or platelet inhibitors. During the infusions, four patients reported headache and one reported chest tightness and neck pain, which resolved with symptomatic treatment. No patient received antihypertensives during the infusion.

See Online for appendix

Our patients had acute intracranial haemorrhage (figure A) after receiving three, four, or five doses of alemtuzumab (figure B), all occurring several hours after leaving the infusion centre. Three patients were found with reduced levels of consciousness by family members; among these three patients, one was found unresponsive the following morning. One patient called the multiple sclerosis centre to report a severe headache overnight and was sent by the covering provider to the emergency department, and another was awake but confused and was diagnosed with a focal neurological deficit by the treating physician (appendix). Four of the five intracranial haemorrhages occurred in the basal ganglia and one in the frontal lobe. All patients required admission to an intensive care unit. Two patients had intraventricular extension and one patient required decompressive hemicraniectomy and external ventricular drain placement. Currently, two patients have recovered well, without residual deficits, whereas three have significant neurological sequelae beyond the deficits related to their multiple sclerosis.

In four of five patients, daily mean systolic blood pressure increased before the day of the intracranial haemorrhage event (figure B). From the first day of infusion to their last infusion day, mean systolic blood pressure increased by 22·0 mmHg (equating to a relative increase of 22·8%) in patient 1, 18·5 mmHg (15·0%) in patient 2, 57·4 mmHg (54·7%) in patient 4, and 24·0 mmHg (23·3%) in patient 5 (appendix). Patient 3 had notably labile blood pressures during the infusion.

The locations of the haemorrhages suggest hypertension as the aetiology, a hypothesis that is supported by the increasing blood pressure measurements before the day of intracranial haemorrhage and by the fluctuations substantially higher than baseline blood pressure in all five patients. In retrospect, this blood pressure increase appears to have been the only identifiable indication of intracranial haemorrhage; two of the patients (patients 1 and 5) were normotensive throughout their period of observation in the infusion centre, and none of the patients had symptoms during infusion outside the expected side-effect profile of alemtuzumab. Alterations in haemodynamics are commonly observed during alemtuzumab administration, most commonly hypotension; hypertension was rarely reported in the clinical trials that tested alemtuzumab in patients with multiple sclerosis.[2–4] The fact that these haemorrhages occurred after-hours suggests that elevations or fluctuations in blood pressure might last several hours following alemtuzumab administration, beyond the monitoring period in the infusion centre.

We believe that patients whose mean systolic blood pressure increases by either 20mmHg or more, or 20% or more throughout the infusion period, or who have a single blood pressure reading that is more than 20% higher than their baseline, might be at high risk of intracranial haemorrhage. If a rising blood pressure trend is observed, physicians could consider inpatient admission for close observation (eg, frequent vital signs and neurological checks, and strict blood pressure control) during alemtuzumab infusion, if the benefits of continuing to administer alemtuzumab are deemed to outweigh the potential risks. Understanding the haemodynamic alterations that occur beyond the typical monitoring period in the infusion centre will be useful to develop the safest administration protocols.

We thank our patients for their willingness and consent for their cases to be reported, and Dr Daniel Pelletier for his critical review and discussion of this Correspondence.

CJA has received consulting fees from Novartis, Sanofi-Genzyme, Biogen Idec, Guerbet LLC, and Genentech; CK has received speaking or consulting fees from Novartis, Sanofi-Genzyme, Teva, Amgen, Biogen Idec, Accorda, and Mallinckrodt, and grants from Sanofi-Genzyme; AD has received personal fees from Biogen, Genzyme, Mallinckrodt, Novartis, Amgen, and Promius; AB has served on advisory boards or served on the speakers' bureau for Biogen Idec, Sanofi-Genzyme, Genentech, Novartis, Medtronic, Neuromodulation, Multiple Sclerosis Association of America, and Peer View; NS has received speaking fees from Genentech and consulting fees from Medtronic; and JK has received speaking fees from Amgen, Allergan, Teva, and Lilly.

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Figure: **Chinese hieroglyphic character for encephalitis**

Pictographs of encephalitis in Chinese characters

Chinese is perhaps the only hieroglyphic language still in use. The oldest Chinese characters are found in oracle inscriptions on bones or tortoise shells of the Shang Dynasty (16th–11th century BC), expressing concepts through hieroglyphic and ideographic forms. But modern medical terms such as encephalitis can also be expressed with Chinese characters.

Encephalitis in Chinese characters is 脑炎, pronounced Nao-Yan. 脑 (Nao), which was a hieroglyph of the head in oracle inscriptions ( or), means brain. Parts of the hieroglyph are , indicating a pouch or a skull, and , indicating cerebral gyrus or hair. is the pictograph of human beings, which indicates that the brain is a part of the human body.

炎 (Yan) was initially written as or and consists of two superimposed flames (火, pronounced Huo). So 炎 is a double flame, representing a violent fire. The double flame 炎 (Yan) might have been named after a tribal leader in ancient China (approximately 5000 BC), Emperor Yan—one of the forefathers of Chinese—after he promoted the use of fire.

Brain on fire: my month of madness, a book by Susannah Cahalan, details her struggle with anti-NMDA-receptor encephalitis. The title of this autobiographical recollection fascinates me, because of its relation with the Chinese characters to express encephalitis, which are a pictograph of a brain on fire (figure).

I declare no competing interest.

I thank Dr Juebin Huang, Department of Neurology/The MIND Center, University of Mississippi Medical Center, Jackson, MS, USA, for his help in revising and proofreading this Correspondence.

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For more on **Susannah Cahalan's book** see **In Context** *Lancet Neurol* 2013; **12:** 337