Case Report

A 5-Year Experience with Medulloblastoma at Queen Sirikit National Institute of Child Health: Case Series

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Objective: To review management and outcome of treatment of medulloblastoma patients over a 5-year period, between 2010 and 2014, at Queen Sirikit National Institute of Child Health (QSNICH).

Materials and Methods: A retrospective case series of medulloblastoma patients treated at QSNICH by the author between 2010 and 2014 was conducted. Demographic data of patients including sex, age at diagnosis, clinical risk stratification, histopathological subtype of medulloblastoma, mode of treatment, complication, and result of treatment were reviewed and discussed.

Results: During the 5-year period, 11 medulloblastoma patients were treated by the author at QSNICH. Six of them were male. Three patients were less than 3-year-old at diagnosis. Five patients were classified as standard risk and six patients were high-risk. Histopathological subtype of medulloblastoma were classic in nine cases, desmoplastic subtype in one case and another case was medulloblastoma with extensive nodularity (MBEN). All patients were operated. Tumor were totally removed in nine cases, confirmed by postoperative magnetic resonance imaging (MRI). After surgery, two cases were referred, and eight cases received adjuvant therapies including radiotherapy and chemotherapy. One case was treated palliatively. Eight patients were able to be followed after treatment. Three patients expired, two of them expired from diseases progression and one expired from complications of treatment. In 2017, three patients lived longer than five years after diagnosis.

Conclusion: Treatment of medulloblastoma at QSNICH has improved during recent years. Morbidity and Mortality of medulloblastoma patients were not only cause by disease itself but also by complication of treatment too. Retrospective review of treatment protocol and outcome of the author's institute are crucial to improve the results of treatment. However, longer followed-up period and more cases are required to be included in future studies.

Keywords: Medulloblastoma, Histopathological subtype, Clinical risk stratification

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Medulloblastomas are the most common malignant brain tumors of childhood, and constitutes 20% of children brain tumor[1]. In United State, the overall incidence rate of Medulloblastomas is approximately 1.5 per million[2]. In Thailand estimated incidence rate of primitive neuroectodermal tumor (PNET) surveyed by the Thai Pediatric Oncology Group between 2003 and 2005 was 2.2 per million[3].

Nowadays, treatment and prognosis of medulloblastomas patients were classified by the risk stratification systems. High risk patients are patients who had postoperative residual tumor more than 1.5 cm^2 on magnetic resonance imaging (MRI), had evidence of disseminated diseases, or were less than 3-year-old at diagnosis. Average risk patients are patients who had postoperative residual tumor less than 1.5 cm^2 on MRI, no evidence of disseminated disease or were older than 3-year-old at diagnosis[4]. The 5-year overall survival rate of medulloblastoma patients had been gradually improved over time with proper treatment. At present, the 5-year overall survival rate is approximately 70% for the average group patients and 50% for the high-risk group[2].

Queen Sirikit National Institute of Child Health (QSNICH) is a public hospital, tertiary care center that focus on caring pediatric patients in Thailand. Neurosurgical service has been available since 1980. Many of medulloblastoma patients have been treated

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Table 1. Demonstrate patient's age at diagnosis, histopathological subtype, number of recurrent, and present conditions

Case No.	First visit	Age at diagnosis	Histopathological subtype	Number of recurrent	Present condition	KPS
1	Dec 2010	9 years 11 months	Classic	0	Healthy	100
2	Feb 2011	6 years	Classic	0	Expired	0
3	May 2011	10 years	Classic	0	Paraplegic	60
4	Jul 2011	11 years 11 months	Classic	0	Expired	0
5	Aug 2011	10 years 10 months	Classic	1	Lost to follow-up	-
6	Feb 2012	1 years 7 months	Desmoplastic	-	Referred after surgery	-
7	Oct 2012	7 years 8 months	Classic	-	Referred after radiation therapy	-
8	Oct 2012	6 months	MBEN	2	Healthy	100
9	Nov 2013	11 years	Classic	0	Ataxia	70
10	Apr 2014	8 years 4 months	Classic	0	Healthy	100
11	Dec 2014	2 years 2 months	Classic	2	Expired	0

KPS=Karnofsky Performance Scale; MBEN=medulloblastoma with extensive nodularity

here but there is no systemic review of patients characteristic, treatment, and treatment outcome. In the present paper, detail information about the patients treated by the author between 2010 and 2015 are retrospectively reviewed.

Materials and Methods

Between 2010 and 2015, the author treated 11 newly diagnosed medulloblastoma cases at QSNICH. After received approval from the Ethical Committee, medical records, operative records, and all medical images of the patients were retrospectively reviewed. Data were collected including sex, age at diagnosis, clinical risk stratification, histological subtype, treatment method, volume of residual tumor on postoperative images, outcome of treatment, evidence of recurrence, patient's condition at present, and Karnofsky Performance Status Scale (KPS) were evaluated. Those data were collected and discussed.

Results

Eleven patients were included in the present study, including six male patients. Patient's characteristic are shown in Table 1. The youngest patient was six months old. The oldest patient was 11 years 11 months. Three patients were less than 3-year-old at diagnosis (n = 3; 27.27%). The mean age was seven years three months old.

Pathological examination of all cases were done at the Institute of Pathology, Department of Medical Services, Ministry of Public Health. For histological subtype, nine cases (n = 9/11; 81.8%) were classic medulloblastoma, one case (n = 1/11; 9.09%) was desmoplastic medulloblastoma, and one case (n = 1/11; 9.09%) was medulloblastoma with extensive nodularity (MBEN). About molecular marker and molecular diagnosis of medulloblastoma, Beta-catenin status were reported in two cases (case No.8 and 11), both were negative nuclear beta-catenin staining.

During followed up period, recurrent of disease was detected in three cases (n = 3/11; 27.27%).

In the present series, three patients expired (n = 3/11; 27.27%). Case No.2 had shown progressive dissemination since the first visited and expired from progressive disease a few months after diagnosis. Case No.4 expired due to *Candida* pneumonia, an acute respiratory distress syndrome and febrile neutropenia after receiving the second course of chemotherapy. Case No.11 expired due to multiple recurrence of tumor and disseminated beyond treatment 22 months after diagnosis.

Two patients (n = 2/11; 18.18%) had morbidity from treatment, case No.3 became paraplegic due to spinal radionecrosis and case No.9 had ataxia due to vermis infarct.

Three cases (n = 3/11; 27.27%) were unable to follow the outcome of treatment, one case was lost to follow-up and two cases were referred to another hospital.

Risk stratification

About clinical risk stratification, six patients (n = 6/11; 54.54%) were stratified as high- risk, details are shown in Table 2. Cerebrospinal fluid (CSF) was sent for examination of dissemination and the result were negative in all cases. Before 2013, there was no MRI

Table 2. Demonstrate Stratified clinical risk of each patients in detail including age at diagnosis, size of residual tumor on postoperative MRI and evidence of dissemination

Case No.	Age at diagnosis	Residual tumor on postoperative image	Evidence of dissemination	Risk
1	9 years 11 months	Less than 1.5 cm^2	No	Average
2	6 years	Only partial tumor removal could be done	Diffused subarachnoid space and spine were disseminated	High
3	10 years	Less than 1.5 cm^2	Suprasellar lesion on MRI	High
4	11 years 11 months	Less than 1.5 cm^2	No	Average
5	10 years 10 months	Less than 1.5 cm^2	No	Average
6	1 years 7 months	3×2×3 cm on CT scan	No data (no MRI image)	High
7	7 years 8 months	Less than 1.5 cm^2	No	Average
8	6 months	Less than 1.5 cm^2	No	High
9	11 years	Less than 1.5 cm^2	No	Average
10	8 years 4 months	Less than 1.5 cm^2	Subarachnoid space at cervical level	High
11	2 years 2 months	Less than 1.5 cm^2	No	High

CT=computerized tomography; MRI=magnetic resonance imaging

unit at QSNICH, so postoperative MRI were done in delay fashion (one month after surgery). After 2013, postoperative MRI was done within 48 hours after surgery. In case No.6, the patient was very young, unstable at perioperative period, and was high-risk to send the patient to perform an MRI scan outside the hospital. Therefore, there is no MRI scan in this case. After his clinical was stable, he was referred to another hospital. In the average risk group, two patients (n = 2/5; 40%) were still alive, two patients (n = 2/5; 40%) were unable to be followed, and one expired (n = 1/5; 20%) from complication of treatment without evidence of recurrence. In high-risk group, three patients (n = 3/6; 50%) were still alive, one patient was unable to be followed, and two patients (n = 2/6; 33.33%) expired.

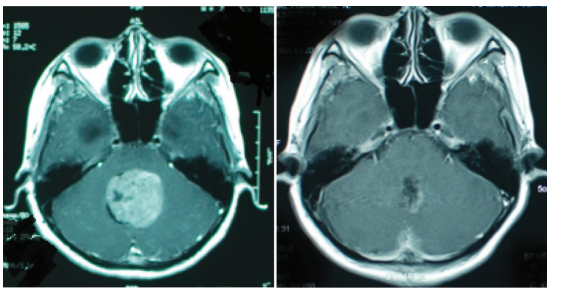

Figure 1. Example of pre and postoperative image of case that achieve gross totally tumor removal. (Left) Preoperative MRI T1 with contrast of case No.4. (Right) Postoperative MRI T1 with contrast.

Treatment

Treatment of medulloblastoma include surgery, chemotherapy, and radiotherapy. All patients received surgical treatment. Post-operative images were obtained either at the fourth week or within 48 hours before other treatment was started. Size of residual tumor was measured from MRI T1 with contrast images. Nine from eleven patients were achieved gross total tumor removal (less than 1.5 cm^3 of residual tumor was observed on postoperative images) as shown in Figure 1.

One case (case No.2) presented with severe disseminated disease and in very poor general condition. Partial of tumor was able to remove, aimed for debulking and getting pathological diagnosis. Preoperative MRI of this case was shown in Figure 2.

Another case that could not achieve gross total tumor removal was case No.6. Tumor size was very large and the deepest part was out of reach at the end of the operation. Postoperative CT scan showed small residual tumor at thalamus. Images are shown in Figure 3.

There was no intraoperative and perioperative mortality in the present case series. Three patients temporary experienced cerebellar mutism syndromes, one case had ataxia from vermis infarct.

About chemotherapy, eight from 11 patients received chemotherapy at QSNICH. Two patients were referred to another hospital. Case No.2, which presented with severe disseminated disease, their parents chose to receive palliative care instead of aggressive adjuvant therapy. Chemotherapeutic regimen prescribed for patients in the present series were the regimen recommended by the Thai Pediatric Oncology Group and consisted of cyclophosphamide, vincristine, high dose methotrexate, carboplatin, and

Table 3. Summary of treatment and complication

Case No.	Postoperative residual tumor	Surgical complication	Radiotherapy	Complication of radiotherapy	Chemotherapy	Complication of chemotherapy
1	Less than 1.5 cm^2	-	Craniospinal	-	Received at QSNICH	-
2	Only partial tumor removal	-	No (palliative treatment)	-	No (palliative treatment)	-
3	Less than 1.5 cm^2	-	Craniospinal	Bilateral temporal radionecrosis, spinal radionecrosis paraplegic	Received at QSNICH	-
4	Less than 1.5 cm^2	Cerebellar mutism	Craniospinal	-	Received at QSNICH	*Candida* pneumonia, ARDS, expired
5	Less than 1.5 cm^2	Cerebellar mutism	Whole brain	Spinal recurrent	Received at QSNICH	-
6	3×2×3 cm	-	Referred	-	Referred	-
7	Less than 1.5 cm^2	-	Craniospinal	-	Referred	-
8	Less than 1.5 cm^2	-	Craniospinal	-	Received at QSNICH	-
9	Less than 1.5 cm^2	Cerebellar mutism, vermis infarct	Craniospinal	-	Received at QSNICH	
10	Less than 1.5 cm^2	-	Craniospinal	-	Received at QSNICH	-
11	Less than 1.5 cm^2	-	Craniospinal	-	Received at QSNICH	-

ARDS=acute respiratory distress syndrome

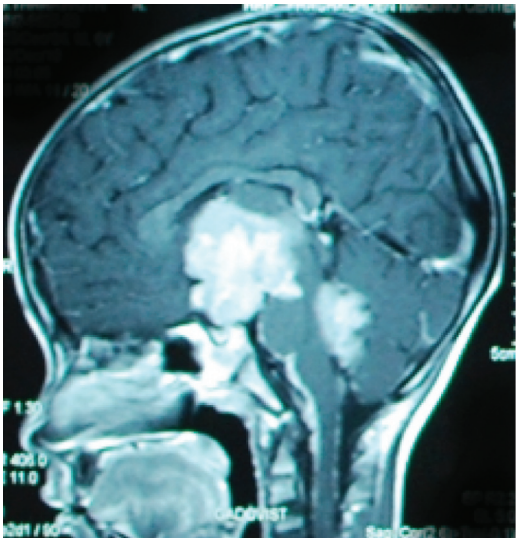

Figure 2. Preoperative MRI T1 with contrast, sagittal view. Showing disseminated tumor involving supra-sellar and 3rd ventricle, 4th ventricle and prepontine subarachnoid space.

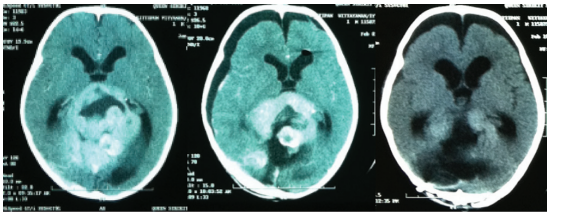

Figure 3. Showing CT scan of case No.6. (Left) Showing large tumor at superior vermis, two-stage operation had been done in this case. (Middle) CT scan after occipital transtentorial approach. (Right) CT scan after supracerebellar approach.

etoposide. All eight cases experienced at least one episode of febrile neutropenia. One case had sepsis, *Candida* pneumonia and acute respiratory distress syndrome; this case expired.

About radiotherapy, QSNICH did not have a radiotherapy department. All cases older than three years old at diagnosis or during follow-up period, were referred to receive radiotherapy at another hospital. Eight cases received craniospinal radiation, one case received only whole brain radiation and had spinal recurrence three years later. One case did not receive radiation therapy due to the parents deciding for palliative treatment. One case was referred to another hospital at postoperative period. About complication of radiotherapy, one case had bilateral temporal radionecrosis that occurred nine months after received radiotherapy. Her clinical was improved after treated with steroid. Two years later, she became paraplegic caused by spinal radionecrosis. Steroid therapy and hyperbaric oxygen therapy did not improve her symptoms. Summary of treatment and complication are shown in Table 3.

Outcome

Patients were followed with clinical examination

every three months, MRI brain every six months, and spinal MRI every 12 months. Three patients had recurrent tumor. Case No.5 had spinal recurrence and was treated by spinal radiotherapy two years after diagnosis. The patient was lost to follow-up after completing the radiotherapy course. Case No.8 had locally recurrent tumor in two episodes, at first year and second year after diagnosis. These were treated with reoperation and chemotherapy. When the patient was 3-year-old, she received radiotherapy and at the last follow-up, five year after diagnosis, she was healthy with no recurrence. Case No.11 had two episodes of local recurrence one year after diagnosis and was treated with surgical removal, and with chemotherapy and radiotherapy when she was 3-year-old. Three months after completing radiotherapy, recurrent tumor and dissemination were found on MRI scan and then clinical deterioration was observed and the patient expired.

In 2017, five patients were followed up by the author, three (n = 3/11; 27.27%) of them had lived longer than five years after diagnosis, three patients were expired, one patient was lost follow-up, two patients were referred to another hospital.

Discussion

Medulloblastomas are the most common malignant brain tumor of childhood. In Thailand, the estimated incidence rate of PNET surveyed by the Thai Pediatric Oncology Group between 2003 and 2005 was 2.2 per million[3].

Many of leading medical schools in Thailand reported in literature about medulloblastoma. Pradniwat et al from Department of Pathology, Faculty of Medicine Siriraj Hospiral, reported about histology subtype of 42 medulloblastoma cases treated at Siriraj Hospital during an eight years period (1998 to 2005)[5]. Likasitwattanakul et al from Department of Pediatric, Chiang Mai University, reported the study of brain tumors in children at Maharaj Nakorn Chiang Mai Hospital. They found 35 cases of cerebellar PNET treated at Maharaj Nakorn Chiang Mai Hospital during a 10 years period[6]. Winaichatsak et al from Ramathibodi Hospital reported survival rate of 22 medulloblastoma patients treated between 1998 and 2005[7].

Between 2010 and 2014, the present author treated 11 newly diagnosed medulloblastoma patients. The best way to evaluate the quality of treatment for medulloblastomas is to evaluate 5-year survival rate. Somehow, in the present study, the number of cases were few and duration of follow-up was too short to estimate the survival rate. However, it is still possible to evaluate the quality of treatment in some aspect.

About surgical treatment for medulloblastoma, the ultimate goal is to totally remove the tumor without damage to normal neural structure. Volume of residual tumor significantly affects the long-term outcome of the patient. When all the patients were put together, regardless of age, stage, or the other factors, 11% more children with tumor residuals of less than 1.5 cm^2 had no tumor progression at 5-year compared with those with residual tumor of more than 1.5 cm^2[8]. In the present case series, nine from 11 patients (81.81%) had residual tumor less than 1.5 cm^2. Most of the cases in the present study were possible to perform gross total tumor removal without perioperative mortality.

The author found that three from 11 patients (27%) had postoperative cerebellar mutism. There was a study that estimated the incidence of postoperative cerebellar mutism. The Children's Oncology Group found that 107 (24%) of 450 medulloblastoma patients had postoperative cerebellar mutism[8].

One patient in the present series had ataxia due to infarction of vermis. This showed that not only normal neural tissue that should be identified and preserved during surgery but also the important vascular structure.

Radiotherapy is important adjuvant for medulloblastoma patients. Radiotherapy is effective in term of local control of medulloblastoma. Previously, the whole cerebellum was irradiated, but recent studies[9,10] demonstrated that conformal boost to tumor bed could achieve similar local control and had less ototoxicity. Recommended dose for tumor bed boost are total dose of 54 to 59.4 Gy. Radiotherapy is also effective in control of micrometastatic disease too. Craniospinal radiation is delivered to entire brain and spine to a total dose of 23.4 Gy. This reduce-dose regimen is well established for pediatric patients[11]. Packer and Vezina had reported progressive disease when received craniospinal dose at 18 Gy compared with 23.4 Gy[4]. Appropriate time for radiation also has impact on the treatment outcome too. Recent studies[12,13] found that radiotherapy in medulloblastoma cases should initiated at 3.1 weeks after operation but not exceed over 90 days for better results.

Unfortunately, QSNICH do not have Radiotherapy Department and all patients have to be referred to other hospital. This made some of the important data such as dose of radiation unavailable. One case did not receive spinal radiation and had spinal recurrent. The other case's complication was cranial and spinal radionecrosis.

Previously, treatment modalities of medulloblastoma consisted of surgery and radiotherapy. Approximately 60% of children were alive and free of progressive disease five years after diagnosis, but many had significant neurocognitive sequelae[14]. Effectiveness of adjuvant chemotherapy in treatment of medulloblastoma was studied, comparing patients randomly assigned to receive radiation therapy with or without adjuvant chemotherapy. The results were children with more extensive tumors, event-free survival was better in the group receiving chemotherapy (48% versus 0%, p=0.006)[15]. By adding adjuvant chemotherapy to medulloblastoma patients can also beneficial in lowering the dose of craniospinal radiation from the traditional dose of 36 to 23.4 Gy. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy were studied and found that the therapy was relatively well tolerated and the progress-free survival at 5 years was 79%[14].

Combined treatment of chemotherapy and radiotherapy after surgery have been proven effective in treatment of medulloblastomas[13-16]. A multi-institutional study showed that treatment with chemotherapy and radiation improved the survival of the patients. The overall 5-year progress-free survival rate was 85% in the study[15]. It was also beneficial in the aspect of lower the risk of neurocognitive sequelae when treated with reduced-dose radiotherapy[17]. All patients continuously treated at QSNICH received chemotherapy, which was well tolerated by all but one patient. One patient had severe sepsis and *Candida* pneumonia. Some case may have severe adverse effect using our standard regimen.

Pathological diagnosis has an important role in predicting prognosis and impact on treatment protocol in the future. There was a study about survival and prognosis of childhood medulloblastoma conducted by Rutkowski et al[18]. It showed that each of histological subtype had different long-term outcome. MBEN and desmoplastic group had better prognosis compared with classic subtype, while anaplastic and large cell medulloblastoma had worst prognosis[18]. Two cases in the present case series were desmoplastic and MBEN subtype. One patient that able to be followed was still alive. However, the number of cases were too small to demonstrate statistical difference between histological subtype group.

In recent years, molecular and genetic knowledge are developing rapidly. Molecular subtype of medulloblastoma was proposed and accurately predicted outcome. In 2016, the World Health Organization Classification of tumor of central nervous system was reclassified as medulloblastoma based on the genetic finding of tumor, into Wnt signaling pathway (WNT)-activated, Sonic hedgehog signaling pathway (SHH)-activated, group 3 and group 4[19]. Evidences from recent studies[20-23] demonstrated that at least four molecular subgroups have difference in transcription profiles, mechanism of tumorigenesis, and clinical outcomes. WNT subgroup has most favorable prognosis, which is found in approximately 10% of medulloblastoma cases. Group 3 has worst prognosis, which is found in approximately 15% of medulloblastoma cases. SHH and group 4 had intermediate prognosis and is found in 30% and 45%, respectively, of medulloblastoma cases. Future treatment options of each subgroups are under investigation. Such as in WNT subgroup which is well response to chemotherapy, has favorable outcome. Treatment protocols for this group are designed to minimize radiation and standard chemotherapy[20]. New treatments that target oncogenic mechanism are under investigating too. Northcott et al[24] suggested the use of panobinostat (a non-selective histone deacetylase inhibitor) (Novartis, USA), since the disruption of chromatin remodeling is thought to play a pivotal role in WNT medulloblastoma. Other example was the study of The Wechsler-Reya group that showed that HDAC and PI3K inhibitor combinations were promising in the models of group 3 medulloblastoma[25]. It will take sometimes before those treatments are well studied and become standard treatments. However, it shows that subgroup molecular classification is crucial in management of medulloblastoma cases. Fortunately, the Institute of Pathology has been performing molecular test for medulloblastoma, beginning with beta-Catenin status of tumor in 2014. It could perform molecular diagnosis in 2016.

For long-term outcome of the present study, three patients were lived longer than five years after diagnosis but other three cases expired, two of them caused by progressive disease and one caused by complication of treatment. Two patients were referred out and one patient was lost follow-up. The author also found that two patients had permanent neurological sequalae caused by complication of treatment.

The present study needs longer time and recruit more cases to evaluate survival rate of the medulloblastoma patients. However, the present case series provides the researchers information about many issues. It showed that there are quite a number of medulloblastoma cases. Gross total tumor removal

can be safely performed in most cases. Morbidities and mortality in the present group of patients have been caused by either treatment complication or disease progression.

The present study shows that patients can live with long disease-free period, however, some patients have expired. Therefore, there are needs to improve the quality of treatment in many issue, such as, lost to follow-up problems and working with radiotherapy in multidisciplinary manners.

Between 2010 and 2014, QSNICH had been improving the management of medulloblastoma. Significant changes included having an in-hospital MRI unit in 2013 to investigate and identified the clinical risk of all the medulloblastoma patients. Another important change was advance in pathological examination of the Institute of Pathology. It helped clinician in predicting prognosis and planning for treatment.

It is challenging to overcome the limitation and improve quality of treatment to meet the international standard.

Conclusion

Treatment of medulloblastoma at QSNICH has been improving during recent year. Morbidity and Mortality of medulloblastoma patients, is not only caused by the disease itself, but also caused by complication of the treatment. Retrospective review of the treatment protocol and outcome of the author's institute are crucial to improve the results of treatment. However, longer follow-up period and more cases should be included in future studies.

What is already known in this topic?

Treatment and outcome of Medulloblastoma were well studied in America and Europe. Some studies had been conducted in medical school in Thailand. Those centers were well equipped with multidisciplinary team.

What this study adds?

This study is the first study about treatment and outcome of medulloblastoma patients from QSNICH, one of many hospitals in Thailand that services rely on referring systems. This study showed the outcome of medulloblastoma patients when standard protocols are applied to the current practice in Thailand.

Acknowledgement

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Conflicts of interest

The author declares no conflict of interest.

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