Central Nervous System Complications from Multiple Courses of the Monoclonal Antibody Muromonab-CD_3 (OKT_3) Therapy: a Case Report

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Abstract: This case report was a 17-year-old Australian boy who had undergone 3 episodes of cadaveric renal transplantations which complicated by two episodes of central nervous system adverse effects from the monoclonal antibody muromonab-CD_3 (OKT_3) during his first and third operation. The duration between the two reactions was 8 years.

บทคัดย่อ: ภาวะแทรกซ้อนทางระบบประสาทเนื่องจากการใช้ยา OKT_3 หลายครั้ง: รายงานผู้ป่วย 1 ราย

กุลฤดี วงศ์เบญจรัตน์ พ.บ.
กลุ่มงานกุมารเวชกรรม โรงพยาบาลมหาราชนครราชสีมา จ.นครราชสีมา 30000
เวชสาร โรงพยาบาลมหาราชนครราชสีมา 2542;23:39-47.

รายงานผู้ป่วยชายชาวออสเตรเลียน อายุ 17 ปี มารับการผ่าตัดเปลี่ยนไต 3 ครั้ง ที่โรงพยาบาลรอแยลชิลเดรน เมืองเมลเบิร์น ประเทศออสเตรเลีย และได้รับยา OKT_3 ทั้งหมด 5 ครั้ง เกิดภาวะแทรกซ้อนทางระบบประสาทจากยา OKT_3 2 ครั้ง ในระหว่างการผ่าตัดเปลี่ยนไตครั้งที่ 1 และ 3 ระยะห่างของการเกิดภาวะแทรกซ้อนทั้งสองครั้งนาน 8 ปี

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Muromonab-CD_3 (orthoclone OKT_3) is a murine monoclonal antibody of IgG_{2a} subclass produced by hybridoma technique that specifically recognizes, binds and blocks the CD_3 antigen recognition complex on the human T-cells surfaces. The interaction results in transient rapid disappearance of circulating T-lymphocytes followed by the emergence of a population of T-cells that are CD_3^+/CD_4^+ or CD_3^+/CD_8^+. These cells appear to have lost the CD_3-T cell receptor (TCR) complex from their surfaces, rendering them immunologically incompetent and no longer able to recognize alloantigen so that OKT_3 can reverse or prevent T-cell mediated rejection responses. After termination of orthoclone OKT_3, T-cell function usually returns to normal within one week.

Since its first randomized, prospective clinical trial for renal transplant rejection in 1981,[1,2,10] the use of OKT_3 has increased widely and now it is approved to be one of the drugs effective in prevention and reversal of solid organ allograft rejection. Besides its effectiveness in treatment, it does have many adverse reactions because whenever OKT_3 engages the CD_3 molecular complex, a transient activation of the T-cells occurs. It has been well documented both in vitro and in vivo studies that OKT_3 - CD_3 mediated T-cell activation is associated with the release of some cytokines such as tumor necrosis factor (TNF- α), interferon gamma, interleukins (IL-2, IL-6, etc) which can produce adverse effects on various organs of the recipients.[3-7] These cytokines are elevated in plasma within 1 to 2 hours after OKT_3 administration and return to the baseline within 24 hours. IL-6 peaks in plasma 48 hours after starting OKT_3 treatment and returns to the baseline by day 4.[8] Other lymphokines and perhaps monocyte-derived peptides may be released also.

Massive release of these cytokines into the circulation occurs within the first and sometimes second dose of OKT_3 while there are large numbers of circulating CD_3^+ T-lymphocyte[3-7] but there are some reports stated the occurrence of these phenomena beyond the second dose of OKT_3.[9]

A well described clinical symptom called cytokine release syndrome (CRS) regularly accompanies these events, so the CRS (first dose reaction) also occurs within 1 to 2 hours after the first and occasionally the second dose of OKT_3.[3-9] Commonly, 80-90% of the patients experience self-limited flu-like symptoms of fever, chill, headache, malaise, joint pain but may also have pulmonary symptoms (dyspnea, tachypnea, and wheezing), cardiovascular symptoms (tachycardia, arrhythmia, hypotension and hypertension), gastrointestinal symptoms (nausea, vomiting, diarrhea and GI hemorrhage), hematological symptoms (pancytopenia and thrombosis), renal symptoms (transient decline in GFR that can lead to delay renal allograft function), neurological symptoms (seizure, aseptic meningitis, cerebritis and encephalopathy). These symptoms are often mild to moderate in severity but life-threatening reactions such as pulmonary edema, severe encephalopathy, heart failure also do occur in 5-7% of the patients. Rarely, an anaphylactic reaction has been observed.[21]

The high number of CD_3 T-cell,[6] higher dose of OKT_3 treatment,[24,29] poor renal function,[18,22,32] increasing the dose or resuming treatment after a hiatus may enhance the appearance of CRS.

The use of OKT_3 in pediatric patients has not

been approved yet since there are many risks from OKT_3 to this group of patients.[43] The pediatric patients were also reported to be significantly immunosuppressed for a longer period of time than adults that may render them to suffer from various opportunistic infections and from infections not commonly occur in adults such as RSV, adenovirus, varicella zoster groups. Because the majority of children have not been infected with these organisms before the transplantation, they are more susceptible to develop primary infection from these organisms in the grafted organ. The children also have higher risk for the development of EBV-associated lympho proliferative disorders (LPD). Although the use of this product in pediatric patients may also increase the complicated risks of thrombosis and pulmonary edema because of the difficulty in body fluid homeostasis control and management, OKT_3 is still being used in some pediatric patients.

One of the most severe complications from OKT_3 is CNS adverse effects.[12-20, 26-28, 41] The most frequently reported CNS adverse effects include seizures, encephalopathy, cerebritis and aseptic meningitis. There were many reports concerned about OKT_3-associated neurological adverse effects but rare cases were reported about the recurrent episodes of these symptoms.[27]

I described a 17-year-old Australian boy who had had 3 episodes of cadaveric renal transplantation and had received multiple courses of OKT_3 therapy for reversal of his renal allograft rejection and for prevention of graft rejection. He then suffered from two episodes of CNS adverse reactions from OKT_3.

Case report

A 17-year-old Australian boy with end stage renal disease (ESRD) had sufferred since he was 8 years old secondary to medullary cystic kidney disease diagnosed when he was 4 years old. He had undergone 3 cadaveric renal transplantation. The first one was done in 1987 when he was 8 years old, the second was done in 1991 when he was 12 years old and the last one was done in 1997 when he was 17 years old.

During his first renal transplant, he developed postoperative acute tubular necrosis (ATN) and had multiple (six) episodes of renal allograft rejections due to his poor immunosuppressive drugs compliance. So for reversal of his first renal allograft rejection which occurred $1^1/_2$ years after the transplant, he received the first OKT_3 course of OKT_3 2.5 mg daily for 10 days due to poor conventional therapy response. After 24 hours of OKT_3 therapy, he developed high fever, neck stiffness, photophobia. A lumbar puncture done revealed clear cerebrospinal fluid, CSF glucose and protein were normal, the pressure was 18 cmH_2O. The CSF cell count revealed 511 WBCs (509 polymorphonuclear cells and 2 lymphocytes). All cultures and stains for bacterial, viral and fungal were negative. Five days later, the symptoms of aseptic meningitis disappeared without sequelae despite the continuation of OKT_3. One year later he had the sixth allograft rejection episode that did not response to conventional therapy again. So he was given OKT_3 (second course) and the dose of OKT_3 was 2.5 mg daily for 12 days with only high fever complication. But OKT_3 failed for reversal of the allograft rejection so he was then placed for a second course of cadaveric renal transplantation in

1991.

He again had 3 episodes of renal allograft rejections during the second transplantation and during the second episode of these three rejections that occurred 1 year after the transplant he was given the third course of OKT_3 again with OKT_3 at dose of 2.5 mg daily for 10 days due to failed conventional therapy. He then developed high fever and hypotension during the therapy but succeeded in reversal of the allograft rejection. Unfortunately, he had the third episode of rejection again 2 months later that failed to response to conventional therapy so that he was given the fourth course of OKT_3 again but OKT_3 had to be ceased within two days because of uncontrolled high fever. So the unfunctioned second cadaveric renal allograft was removed in few days later.

He was placed for the third course of cadaveric renal transplant in 1997. During the time he was given OKT_3 (fifth course) in order to prevent renal allograft rejection due to his high panel reactive antibody (PRA > 50%). The OKT_3 dose was 5 mg daily and the first dose was given during operation at the time of commencement of venous anastomosis. Postoperatively, he developed high fever, hypertension which converted to hypotension in the second post operative day. OKT_3 was ceased at that time due to presumed adverse reactions from it. During the third postoperative day he was given OKT_3 again and later developed fever, headache, neck stiffness and conscious change in the next day (the fourth post operative day). The conscious change was beginning with blurred eye, dizziness, drowsy and hallucination that progressed slowly to coma with poor muscle tone, hyperreflexia and extensor plantar response but no papilledema. The lumbar puncture revealed clear cerebrospinal fluid with normal glucose value but slightly elevated protein level. The CSF cell count had 207 WBCs (129 polymorphonuclear cells and 78 lymphocytes). All cultures and antigen detection for bacterial, viral and fungal organisms were negative. He was then sent for CT scan that was also normal. The EEG done at that time was compatible with severe encephalopathy.

He began to have low urine output so he was sent for renal biopsy that showed acute tubular necrosis with no obstruction, leakage or thrombosis proved by diethylenetriamine pentaacetic acid (DTPA) scan.

The OKT_3 was ceased again during the fourth postoperative day and he was placed on hemodialysis due to his poor renal function and was transferred to intensive care unit. He was intubated and treated with dexamethasone and mannitol and gradually improved in his conscious to fully recovered conscious on the eighth day of the symptoms (12 days postoperation).

So he was prescribed on anti T-lymphocyte globulin (ATGAM) instead of OKT_3 and was discharged from the hospital on the twentieth day post operation with a serum creatinine of 0.86 mg/dL and fair renal function.

DISCUSSION

The patient had undergone 3 times cadaveric renal transplantation in 1987, 1991 and 1997 when he was 8, 12 and 17 years old. He was prescribed on OKT_3 five times. The first OKT_3 treatment course was in 1989 when he had his first renal allograft rejection during his first renal transplantation. The renal allograft rejection

at that time could be reversed successfully by OKT_3. The aseptic meningitis reaction occurred after he was treated with OKT_3 for 24 hours and resolved without sequelae within 5 days despite continuing OKT_3 treatment.

The second course of OKT_3 was prescribed 1 year later to reverse his sixth renal allograft rejection during his first renal transplantation but it failed to reverse the rejection. At that time he had only high fever complication from OKT_3.

The third course of OKT_3 was prescribed 2 years later again to reverse his second renal allograft rejection during his second renal transplantation. The OKT_3 worked successfully at that time with only high fever and some degree of hypotension that responsed to fluid therapy.

Two months later, he was prescribed on the fourth course of OKT_3 again but it had to be ceased within 2 days because of uncontrolled high fever complication.

He was then prescribed on OKT_3 again 5 years later (the fifth course) to prevent renal allograft rejection because of his high panel reactive antibody during his third renal transplantation. At this time he again had aseptic meningitis complication from OKT_3 during the fourth postoperative day which complicated by severe encephalopathy that progressed slowly to coma. This reaction occurred 8 years apart from the first aseptic meningitis complication.

There are many reports concerning CNS adverse reactions from OKT_3 [12-20,26-28,41] and common reactions are seizure, cerebritis, aseptic meningitis and encephalopathy. The incidence of aseptic meningitis ranged from 3-15% of the patients treated with OKT_3. The symptoms were fever (89%), headache (44%), neck stiffness (14%), photophobia (10%) and the combination of these symptoms were found only 5%. Fever, headache, CSF pleocytosis with elevated protein level and normal glucose profile with negative CSF cultures are diagnostic clues of aseptic meningitis and typically develop within 24-120 hours after initiation of OKT_3 therapy as in our patient the first aseptic meningitis reaction occurred within 24 hours, the second reaction occurred within 96 hours post OKT_3 therapy.

Martin et al prospectively identified 3 of 21 OKT_3 treated patients (14%) who developed aseptic meningitis within 72 hours of treatments,[19] In another study, 4 of 122 OKT_3 treated patients (3%) developed aseptic meningitis.[11] Roden et al described 3 patients with confusion in addition to meningeal signs and CSF pleocytosis that indicated diffuse parenchymal involvement and meningeal inflammation consistent with cerebritis.[13] Most patients with aseptic meningitis syndrome had a benign course and recovered without any permanent sequelae within 3-5 days despite continuation of OKT_3 therapy[19] as in our patient in his first aseptic meningitis. Approximately one-third of the patients with aseptic meningitis had coexisting signs and symptoms of encephalopathy as same as our patient, (in his second course of aseptic meningitis from OKT_3).[14-18,20] Chan et al reported seven cases of encephalopathy and aseptic meningitis complication from OKT_3 in renal transplanted patients including one case with irreversible blindness.[14] All seven patients experienced delayed graft function. More recently Shihab and coworkers reported 247 patients treated with OKT_3

with 6.9 % incidence of cytokine related encephalopathy observed during 1-4 postoperative days.[18] Interestingly, most patients received less than the usual OKT_3 dose of 5 mg/day. Of these patients, 71% had delayed graft function (DGF), 65% had insulin dependent diabetes mellitus, 47% had a prior history of CNS problems. The incidence of encephalopathy in the diabetes and DGF groups were 56%. Manifestations of encephalopathy included impaired cognition, obtundation, altered mental status, auditory/visual hallucinations, psychosis (delirium, paranoid), mood changes (mania, agitation and combativeness), diffuse hypotonia, hyperreflexia, myoclonus, tremor, asterexis, involuntary movement, major motor seizure, lethargy, stupor and coma.

Radiologic evidence from CT scan of encephalopathy patients have been reported in a few patients.[14,20] These included cortical atrophy, generalized brain edema but in several patients as in our case the CT scan revealed no abnormal findings. Focal abnormalities in CT scan and MRI had also been reported.[28]

How OKT_3 causes encephalopathy remains unclear. Encephalopathy may result from an interaction between OKT_3 and antigens shared by lymphocytes and CNS cells.[46] Alternately, cytokines released from T lymphocytes after injection of OKT_3 may play roles. Cytokines that may have possible roles are TNF and IL-6.[15,18,27,30] The intact blood-brain barrier (BBB) would ordinary preclude these effects, the high risk of complication in uremic patients and DGF patients may occur because these patients may have impaired BBB[31] and also the poor renal function that may precipitate the reaction by retention of the cytokines.[14,18,32] As in our patient he also had poor renal function and also had the obviously higher complicated risk from cadaveric-donor transplantation than living-donor one.[40]

Another risk factor for CNS adverse efflcts is diabetes, especially with delayed graft function, due to abnormal capillaries that is susceptible to leakage upon the release of cytokines.[18] Other risk factors are previous CNS problems,[18] serum electrolytes disturbance disturbances, concomittant drugs such as cyclosporin A, indomethacin, acyclovir, etc.[14,18]

In contrast to aseptic meningitis complication from OKT_3, encephalopathy induced by the drug does not appear to be self-limited. The continuation of OKT_3 may worsen the encephalopathy and the long term consequences of encephalopathy induced by the drug remains unknown,[42] so many experts recommend to cease OKT_3 if the symptoms of encephalopathy occurred, as in our patient we decided to cease OKT_3 in the day the encephalopathy developed.

The current methods that are used to minimize the symptoms of CRS are pretreatment with steroid and antihistamines,[23] but it is clear from many reports that these regimens are inadequate pretreatment for prevention of serious adverse effects from OKT_3 in a significant majority of patients. The other method available is to ameliorate the risk factors described above as for patients with DGF or poor renal function due to severe rejection as in our patient should be placed for early dialysis or hemofiltration in order to prevent or minimize the adverse effects from OKT_3.[18,25,30,32]

It appeared that the new methods to reduce cytokines release from T-lymphocytes could help reducing the adverse effects from OKT_3.[18,23,30] These

methods are OKT_3 escalating dose regimens,[33] method to reduce initial dose of OKT_3 followed by adjusted doses based on CD_3 T-lymphocyte count,[34] low dose OKT_3 induction therapy,[24,29,35,37] pentoxyfylline treated to reduce TNF,[36] TNF-receptor treatment,[38] monoclonal antihuman TNF-α antibody,[47] monovalent anti-CD_3 antibody.[39] Which method is better remains in further investigations.

The occurrence of CNS adverse effects from OKT_3 for more than one occasion in the same patient have rarely been reported.[27] It may be related to the fact that few patients receive many courses of OKT_3 and few had mutiple courses of cadaveric transplantation. Usually, the patients treated with OKT_3 develop antibodies to it within 3 weeks (21% for IgM, 80% for IgG, 29% for IgE), but for our patient we did not look for the antibody and the plasma level of OKT_3[45] (the adequate plasma level of OKT_3 is more than 800 ng/ml) so we could not explain why the reactions occurred and whether he had enough level of OKT_3 or antibodies to it or not. The further studies that detect the plasma level of OKT_3 and antibody to it may be needed.

Conclusion

The monoclonal antibody muromonab-CD_3 (OKT_3) is one of the drugs effective in prevention and reversal of allograft rejection despite its many adverse effects. CNS adverse effects are among one of its severe adverse effects.

I reported a patient with recurrent CNS adverse effects from multiple courses of OKT_3 and we do need the further longitudinal studies of the outcomes following resuming OKT_3 therapy in patients prior experienced with severe adverse reactions from it to determine whether there will be the risk or benefit from using it in that circumstance.

Acknowledgment

I would like to thank Dr. Colin L Jones and Dr. Harley R Powell from Victorian Pediatric Renal Services, Royal Children's Hospital, Melbourne, Australia for their dedication in taking care of the patient, assistance in review of my article and I would also like to thank Baromratchanok Institute, Ministry of Public Health for fund support.

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