

Annex: Summaries of Fatal Cases

MCN 30699: DEATH OF UNKNOWN CAUSE

A 44-year-old female patient expired on 26 Dec 1997. The exact cause of death is unknown since no autopsy was performed. The patient received her first infusion of MABTHERA on 26 Dec 1997 for non-Hodgkin's lymphoma. The patient was pre-medicated with Benadryl, Decadron and Tylenol. MABTHERA 700 mg was infused over five and one-half hours, starting at a rate of 50 ml/hour at a 1.4 mg/ml concentration. The infusion rate was gradually increased. The patient developed chills approximately forty minutes after the infusion was started, and she was treated with meperidine. The patient experienced vomiting approximately two hours after the infusion was started. Approximately one hour later, the patient developed minor dyspnea. The patient apparently continued to experience intermittent dyspnea for the remainder of the infusion. During the infusion, the patient's diastolic blood pressure fluctuated, but the systolic pressure remained stable in the 108 to 120 mm Hg range. The patient was discharged approximately thirty minutes after completion of the infusion. The patient apparently slept while being driven home. Shortly after arriving at home which was approximately one hour after leaving the outpatient infusion facility, the patient collapsed. Paramedics were called, and the patient's condition apparently stabilised while she was transported by ambulance to the emergency room of a local hospital. The patient experienced a cardiopulmonary arrest shortly after arrival in the emergency room and could not be resuscitated. Further follow-up information is expected.

Follow-up information received from the treating physician on 23 Jan 1998 and 04 Feb 1998 indicated that the patient had bulky disease regarding her non-Hodgkin's lymphoma. A left ureteral shunt was placed due to obstructive uropathy secondary to intraabdominal lymphoma. Her creatinine level approximately three days prior to the MABTHERA infusion was 5.0 mg/dl. Electrolytes were unremarkable at that time. No laboratory work was performed immediately prior to or after the MABTHERA infusion. The patient had no known drug allergies. She was receiving an oral hypoglycaemic agent for Type II diabetes mellitus. Approximately 40 minutes after the start of the MABTHERA infusion, the patient developed a shaking chill which responded to meperidine. She also experienced a low-grade fever. The patient's blood pressure was stable throughout the infusion. The patient's mild dyspnea, which occurred during the latter part of the infusion, resolved by the end of the infusion. Her lungs were clear throughout the infusion with no wheezing. After discharge from the infusion facility, the patient arrived at home, where she fell to the floor after entering her house. The patient's father could not find a pulse, and she was not breathing. He performed cardiopulmonary resuscitation. When the paramedics arrived at the home, the patient was breathing spontaneously. She did not require intubation. During her transport to the emergency room the patient was alert and conversing. Upon arrival in the emergency room, the patient quickly lost consciousness and was found to have ventricular tachycardia. Cardiopulmonary resuscitation was instituted. However, the patient did not regain a stable cardiac rhythm, and her blood pressure could not be maintained. The patient was pronounced dead and taken to a funeral home before an autopsy could be performed. The treating physician felt that the sequence of events suggested an abrupt event such as a pulmonary embolus or myocardial infarction, rather than an effect related to MABTHERA. Additional information is expected regarding the patient's clinical course in the infusion facility and the emergency department. More information regarding her laboratory studies is also expected.

Laboratory Data

The patient reportedly had an elevated white blood cell count and a creatinine value of 7.0 mg/dl (unconfirmed at this time).

Follow-up information revealed:

23 Dec 1997 (estimated date) Creatinine level: 5.0 mg/dl

Electrolytes: Unremarkable

Hemoglobin: 7.5 g/dl

WBC: 50,000 to 60,000/microliter (predominantly lymphocytes)

Platelet count: 50,000 to 60,000/cu mm

Relevant Medical History

The patient reportedly has a history of renal insufficiency due to obstructive uropathy secondary to intraabdominal lymphoma, type II diabetes mellitus, chronic anaemia, and episodes of anxiety associated with shortness of breath.

COMPANY COMMENT: This case is well documented.

MCN 90358: RESPIRATORY FAILURE

A 60-year-old female patient received her first infusion of MABTHERA on 26 Feb 1998 for treatment of non-Hodgkin's lymphoma. Shortly after the MABTHERA infusion was started, the patient developed severe bronchospasm. MABTHERA was stopped and then re-started at a slower infusion rate. The patient's severe respiratory distress with bronchospasm continued. The MABTHERA was stopped, and the patient was taken to a hospital emergency room by paramedics.

The patient developed coughing followed by some pulmonary hemorrhaging. The patient was admitted to the hospital. She expired within 24 hours from apparent respiratory failure, although the cause of death was not reported. The patient's oncologist reportedly felt that the event was unrelated to MABTHERA. Further information about this case is expected.

More information obtained from a company representative on 08 Apr 98 indicated that the patient was probably in her 40s (exact age unknown). The treating physician does not feel that the event is related to MABTHERA. Additional clinical information is not available from the treating physician.

The patient had a low platelet count prior to receiving MABTHERA.

COMPANY COMMENT: The dose of MABTHERA and rate of administration are not known. It is not known whether this patient was appropriately pre-medicated. We cannot obtain additional information from the treating physician.

MCN 90507: RESPIRATORY FAILURE

An elderly patient (age unknown) with chronic lymphocytic leukemia developed respiratory failure and died after receiving the first infusion of MABTHERA. The patient apparently became febrile during the infusion and developed dyspnea. The patient then developed bilateral pulmonary infiltrates and died of respiratory failure within 24 hours after completing

... MABTHERA infusion. At the time of this report, no other information was available. The reporting physician had heard about this patient from another physician.

COMPANY COMMENT: This patient received MABTHERA for a non-approved indication. The dose of MABTHERA and rate of administration are not known. This case was provided to the company as second hand information. The reporter was going to try to obtain additional case details from the treating physician.

MCN 90735: DEATH OF UNKNOWN CAUSE

A patient (gender and age unknown) developed hypotension at some point after receiving a MABTHERA infusion (treatment start date, dose regimen and indication not reported). The patient was subsequently admitted to the hospital but died within 24 hours after admission. The cause of death is unknown, and no other case details are available. More information about this case is expected.

COMPANY COMMENT: This case was reported as second hand information at a focus group meeting of oncologists. The name and address of the treating physician was not known at the time. We will try to identify the treating physician to obtain additional case details.

MCN 91137: ADULT RESPIRATORY DISTRESS SYNDROME

A 52-year-old male patient developed Adult Respiratory Distress Syndrome (ARDS) and expired eight hours later on 11 July 1998. The patient received his first infusion of MABTHERA on 09 July 1998 for low-grade non-Hodgkin's lymphoma. The patient received 700 mg of MABTHERA during this six-hour infusion. The patient experienced chills, and tightness of the chest during the infusion, which required a decrease in the infusion rate. Treatment included intravenous Benadryl and Decadron (80 mg) and Demerol. On 10 July 1998 the patient was stable clinically.

On 11 July 1998 the patient was admitted to the hospital with respiratory failure. The patient's clinical picture was consistent with ARDS. The patient was intubated in the intensive care unit. Hypotension and fever were noted. His chest x-ray revealed interstitial infiltrates. Arterial blood gases confirmed that the patient was in respiratory failure. The patient expired eight hours later (two days after the MABTHERA infusion). The patient's physician indicated that there was a reasonable probability that the event was related to MABTHERA, and noted that the event could be related to sepsis, but that the patient's culture results remain negative. Follow-up information has been actively pursued.

COMPANY COMMENT: The case details are reasonably complete.

MCN 91526: MULTIPLE ORGAN FAILURE

A 76-year-old female patient with chronic lymphocytic leukaemia developed multiple organ failure and died after receiving her first MABTHERA infusion. The patient was admitted to the hospital on 23 September 1998 with a decreased white blood cell count (907/microliter) and started her first MABTHERA infusion. She was premedicated with Benadryl and Tylenol. During the infusion, the patient experienced severe lower back pain, and she was treated with Vicodin. A few hours later, her WBC decreased to 460/microliter and her platelet count also decreased from 18,000 to 8,000/microliter. The MABTHERA was

discontinued. The patient was felt to have tumour lysis syndrome with severe acidosis. She required haemodialysis several times. The patient subsequently developed evidence for multiple organ failure and died on 30 September 1998. Her family had decided not to continue dialysis or other interventions. The event was reported as being possibly related to MABTHERA and to tumour lysis from her chronic lymphocytic leukaemia. More information is expected.

Laboratory Data:

Calcium: 7.7 mg/dL on 23 Sep 98 at 20:30 hr; 7.1 on 24 Sep at 19:53 hr; 7.6 on 26 Sep at 13:30 hr.

Phosphorous: 7.1 mg/dL on 23 Sep at 20:30 hr; 6.8 on 25 Sep at 17:58 hr; 8.1 on 27 Sep at 13:30 hr.

Uric Acid: 11.7 mg/dL on 23 Sep at 20:30 hr; 10.9 on 24 Sep at 10:28 hr; 9.4 on 25 Sep at 17:58 hr; 10.2 on 27 Sep at 17:00 hr.

Potassium: 5.7 meq/L on 23 Sep, 3.5 on 24 Sep; 3.0 on 26 Sep; 4.5 on 28 Sep.

Creatinine: 1.1 mg/dL on 23 Sep; 1.2 on 24 Sep; 0.9 on 25 Sep; 1.1 on 27 Sep; 1.2 on 28 Sep.

Blood urea nitrogen: 16 mg/dL on 23 Sep; 23 on 24 Sep; 29 on 25 Sep; 14 on 26 Sep; 20 on 28 Sep

Concomitant Drugs:

Folic acid; Heparin sodium; Nystatin; Vicodin (acetaminophen/ hydrocodone bitartrate; MSO4 (Morphine sulphate)

Relevant History:

The patient had a history of CLL for 19 years. She had an anaemia-related myocardial infarction, haemolytic anaemia secondary to Fludarabine, and a history of colitis. She had a splenectomy performed in the past.

MCN 91532: RESPIRATORY FAILURE

A 53-year-old female patient expired due to respiratory failure on 15 July 1998 during a MABTHERA infusion. The patient's infusion of 625 mg/500 ml normal saline was started at 11:00 on 15 July 1998 for treatment of mantle cell lymphoma. The patient subsequently developed facial itching, shortness of breath, increased crackles in the lungs, decreased oxygen saturation, and pulmonary edema. The infusion rate was increased and decreased dependent upon the patient's tolerance. The patient received a total of 100 mg of the prescribed MABTHERA dose. The patient apparently did not develop bronchospasm or urticaria. The patient expired due to respiratory failure on the same day as MABTHERA infusion. More information has been requested from the reporter.

Follow-up information received on 29 Oct 1998 indicated that on 15 July 1998 prior to the MABTHERA infusion the patient was noted to be in a debilitated condition. The liver was enlarged, and extended approximately eight centimetres below the right costal margin. The patient was alert and oriented. Creatinine was 1.1 mg/dl, WBC 600,000/mm³, and haematocrit was 30 percent. At 11:55 the MABTHERA infusion was started at the rate of 25 cc/hour. At 12:02 the patient complained of an itching throat and MABTHERA was interrupted. At 12:20 the infusion was resumed at 12 cc/hour, then increased to 24 cc/hour at 14:18, and to 49 cc/hour at 15:05. Within five minutes the patient complained of flushing and was light headed, at which time MABTHERA was interrupted. At 15:30 the patient

experienced tingling in the hand. At 15:45 MABTHERA was restarted at 25 cc/hour. At 16:30 the patient experienced numbness. MABTHERA was interrupted. Treatment included Benadryl and Tylenol. At 17:10 the infusion was restarted at 25 cc/hour. At 18:20 the patient experienced wheezing and was given intravenous Solu-Cortef 100 mg. MABTHERA was interrupted, then restarted again at 19:10. At 19:35 the patient developed chest pressure, wheezing, and audible crackles in the lungs. Treatment included Zantac and Benadryl. MABTHERA was stopped. At 19:37 the patient developed tachycardia and oxygen saturations decreased to 87 percent. Oxygen was started. Her creatinine was 1.6 at that time, and the patient was treated with hydration. Oxygen saturations continued to decrease, and the patient became hypotensive and developed increased fluid in the lungs. Treatment included bronchodilators, diuretics, and antibiotics. The patient's condition continued to deteriorate rapidly. The patient was intubated and developed electromechanical dissociation. Cardiopulmonary resuscitation was performed. Epinephrine and dopamine were given. The patient was severely obtunded, with no renal output noted. Life support was discontinued.

Laboratory Data

In addition to above, the following are after the patient received MABTHERA:

Platelet count - 106,000/mm³

AST - 322

Alkaline phosphatase - 327

Relevant Medical History

The patient's history indicated prior chemotherapy agents of Cytoxan, Vincristine and Prednisone (dates of administration not reported). The patient had a known drug allergy to penicillin. There was no apparent history of cardiac disease.

Follow-up information received on 29 Oct 1998 indicated that mantle cell lymphoma was diagnosed in 1995 with atypical lymphocytosis, eosinophilia and lymphadenopathy. In Jan 1998 treatment with Cytoxan, vincristine and prednisone was initiated, followed by experimental treatment with flavopiridol. The patient's white blood cell counts continued to progressively increase.

COMPANY COMMENT: This patient received MABTHERA for a non-approved indication. This case is well documented.

MCN 91726: CARDIOGENIC SHOCK

A 66-year-old male patient experienced cardiac failure on 14 Oct 1998 during his first MABTHERA infusion for non-Hodgkin's lymphoma and later developed cardiogenic shock and died. The MABTHERA infusion was administered at the rate of 45 mg per hour. After 30 minutes, the infusion rate was increased to 70 mg per hour. The patient then experienced atrial tachycardia of 150 beats per minute, hypertension, dyspnea and pulmonary edema. He was felt to have developed cardiac failure. Treatment included Atarax, Solu-medrol, Linitral, Digoxin and Cordarone. The patient's condition improved with return of a normal cardiac rhythm and blood pressure. However, the patient's dyspnea persisted. On 16 Oct 1998 his dyspnea was still present and was associated with a decrease in arterial pressure.

On 17 Oct 1998 he expired with a diagnosis of hyperkinetic cardiogenic shock (three days after the MABTHERA infusion). The report was received from national regulatory authorities, and they apparently felt that the patient's death was related to his underlying

condition. The patient had no history of cardiac disease but did have a recurrent pleural effusion secondary to his lymphoma.

Relevant Medical History

The patient's history indicated that his lymphoma was diagnosed in 1992. He has had a recurrent pleural effusion secondary to the lymphoma. Prior chemotherapy included CHOP, CNOP, and VIM. In April 1997 the patient experienced a relapse of his lymphoma with a pleural effusion. In July and Aug 1998 the patient received the chemotherapeutic agents Novantrone and Fludarabine.

COMPANY COMMENT: This case is reasonably well documented.