Fatal Liver Failure due to Gemcitabine in a Patient with Metastatic Breast Cancer Receiving Palliative Care

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(All speakers have disclosed no relevant financial relationships)

Objectives
1. Recognize potential fatal liver toxicity of gemcitabine in cancer patients receiving palliative care.
2. Discuss plan of care with cancer patients and their families by sharing the knowledge of potential toxicity of commonly used palliative chemotherapy.

Background. With the increasing recognition of the value of palliative care consultation, palliative care specialists have become involved in cancer care much earlier in the disease trajectory. It is therefore important for the palliative care specialists to be familiar with the potential toxicities of commonly used chemotherapeutic agents. To raise awareness of potential hepatotoxicity of gemcitabine in patients receiving palliative care, we report a case of fatal liver failure as a result of gemcitabine treatment in a patient with metastatic breast cancer who was recently started on methadone.

Case Description. A 58-year-old female with a metastatic breast cancer had received gemcitabine for 3 months. Her pain related to skeletal metastases was managed by a palliative care service. Four weeks after the last gemcitabine dose and 2 weeks after initiation of methadone, she was found to have elevated liver function tests (LFT). She had no other change in her medications. Serologic tests for viral hepatitis were negative. Imaging studies showed no hepatic or biliary lesions. Liver biopsy displayed an acute hepatitis which involved the lobules and portal zones with evidence of cholangitis and bile duct proliferation, consistent with drug toxicity. Over the next 2 weeks, her LFTs had worsened progressively, with total bilirubin elevated to 15.3 mg/dl. She also developed encephalopathy and coagulopathy requiring admission to the hospital. Despite maximal supportive care, the liver failure rapidly worsened and kidney function deteriorated. She died in multorgan failure 4 days after the admission.

Conclusion. Only five cases of fatal liver failure have been reported associated with the use of gemcitabine. There is no known drug interaction between gemcitabine and methadone. Gemcitabine can be a contributor to an unpredictable death in patients receiving palliative care. Improved awareness of the potential fatal toxicity of some chemotherapeutic agents may help patients and families define more realistic plan of care.

Domain
Physical Aspects of Care
Fatal Liver Failure due to Gemcitabine in a Patient with Metastatic Breast Cancer Receiving Palliative Care

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Background
• The expertise of specialist-level palliative care has been increasingly recognized
• As a result, we are involved in the care of cancer patients earlier in the disease trajectory
• It is paramount to familiarize ourselves in the care of uncommon, but life-threatening toxicities of chemotherapeutic agents

Case
Cancer History
• A 58 yo woman
  – Bilateral breast cancer
    • Diagnosed in 2002
    • Bilateral mastectomy → chemoradiation
  – 6/08 progressive bone metastases
    • Gemcitabine 1000 mg started
      – Days 1 and 8 of each 21-day cycle
    • Last dose: 9/23/08
Case Gemcitabine

- Gemcitabine
  - 10/6/08 held due to pancytopenia / confusion
  - 10/13/08 held due to confusion/falls x3-4/wk
  - 10/14/08 – 10/17/08
    - Admission with delirium
    - MRI brain: no metastasis
    - Palliative care consulted for pain and delirium
      - Opioid rotation from Oxycodone to methadone
    - 11/6/08 chemo held due to high bilirubin

Case LFT Elevation

- New development of LFT elevation with hyperbilirubinemia
  - No new meds other than methadone and gemcitabine
  - No eosinophilia
  - Hepatitis panel (-)
  - Ultrasound and CT of abdomen/pelvis
    - No focal liver lesions, ductal dilatation or cholecystitis

Case Liver Biopsy

- 11/10/08 Transjugular hepatic biopsy
  - Severe acute hepatitis
    - Involving the lobules and portal zones with evidence of cholangitis and bile duct proliferation
    - The trichrome stains: portal and mild lobular fibrosis
    - The iron stain: significant iron deposition both within the hepatocytes and the Kupffer cells
    - The PAS stain: no significant PAS-positive material
  - Given the clinical history of chemotherapy, the findings are likely drug related
Case Acute Liver Failure

• 11/19/08-
  – Hospital admission w/ AMS, ataxia, and worsening LFTs
  • AST 192 ALT 44 ALP 365 T-bil 15.5
  • Repeated US
    – Moderate ascites, no CBD dilatation; nl portal vein flow
    – Paracentesis: no SBP, no malignancy
  – GI consult
    • Drug-induced acute liver failure
      – Most likely due to gemcitabine
    • Supportive care recommended

Case Hospital Course

• Optimization of the fluid balance and supportive measures

• Liver failure rapidly worsened
  – New ARF, worsened coagulopathy
  – Progressive mental status change
  – DNR → EOL care
  – Died w/ MOF 4 days after the admission
Discussions

• Drug-induced Acute Liver Failure (ALF)
  – Epidemiology
  – Risk factors
  – Clinical manifestations and natural course
  – Treatment

• Fatal ALF caused by gemcitabine
  – Review of 5 cases in the literature
  – Clinical implications in palliative care

Conclusions

ALF Caused by Drugs

• ALF although uncommon, is a devastating syndrome that result in death or the need for a liver transplant in over 50% of cases

• Acetaminophen toxicity and idiosyncratic drug reactions play major roles

• Pts w/ ALF due to idiosyncratic DILI (drug-induced liver injury) is difficult to diagnose and have a lower likelihood of spontaneous recovery

Conclusions

ALF caused by chemo (cont.)

• Uncommon, but potentially fatal consequence
• This is the 6th case of ALF associated with gemcitabine in the literature
• Gemcitabine should be included in the DDx of cholestasis/VOD during chemo
• Comprehensive assessment without delay is vital for newly elevated LFTs in advanced cancer patients on chemo
• Early detection of ALF and timely initiation of proactive supportive care are essential
Conclusions
ALF caused by chemo (cont.)

• Given the contraindication to transplant and high mortality rate, involvement of a palliative care service must be considered

• Recognition of poor prognosis allows oncologists and palliative care specialists to share more realistic expectations with patients, and discuss appropriate care plans with patients and families earlier in the admission process, or even as outpatient.