Long-term Survival Case Report Of Two Pediatric Relapsed Or Refractory Acute Myeloid Leukemia Patients Treated With Bisantrene Combination Therapy

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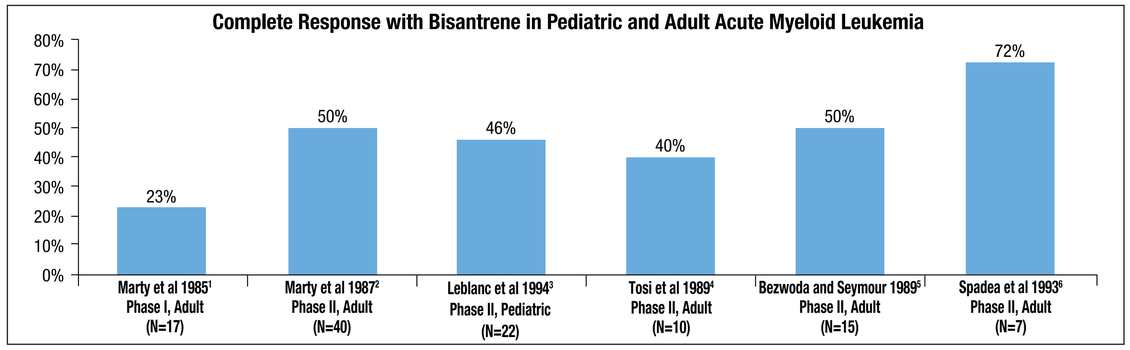
BACKGROUND

- Bisantrene is a less toxic substituted anthracene derivative of the anthracycline class. In addition to DNA intercalation, it activates cytotoxic tumour directed macrophages, is an inhibitor of DNA topoisomerase II enzymes, and can interfere with the function of telomerase.
- Significantly, bisantrene appears to lack classical limitations of anthracyclines, notably dose-dependent cardiotoxicity and anthracycline-induced multi-drug resistance.
- Bisantrene has demonstrated clinical activity in AML with historical CR rates in recurrent or refractory AML ranging from 23% to 72%.[1-6] In one pediatric study, 46% of heavily pretreated pediatric AML patients with poor hematologic status achieved historical CR after treatment with bisantrene + cytarabine (Figure 1).[3]
- We report on two pediatric relapsed or refractory (R/R) AML survivors decades after the study.

FIGURE 1. Historical CR rates reported for bisantrene in pediatric and adult r/r AML.



CASE REPORT

CASE 1. Patient A

Born: May 1977
Sex: Female

AML diagnosis date: Dec 1990 (Figure 2)

- Presented with a white blood cell count (WBC) of 46,500
- Diagnosed with AML type M1 with translocation t(8 ;21)
- Received protocol LAME91
- Achieved CR on Day Jan 1991.
- First consolidation cycle began Feb 1991
- Second consolidation cycle began Mar 1991
- Bone marrow cryopreservation after Asta-Z on Jun 1991

Relapse date: Nov 1991

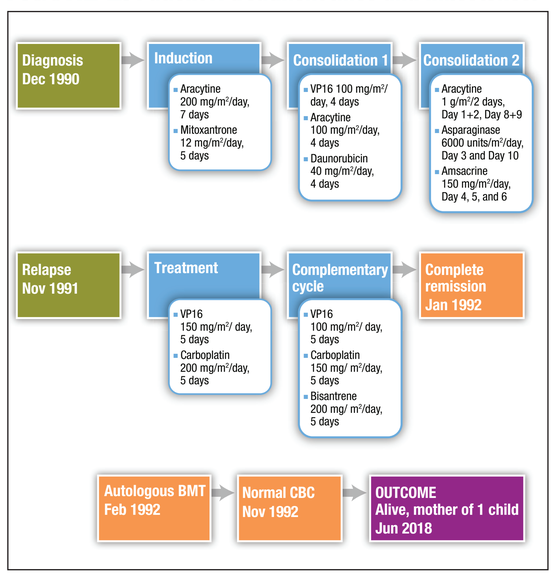
- Treatment initiated Nov 1991
- Myelogram on Day 22 (Dec 1991) revealed poor bone marrow with 70% of blasts
- Complementary cycle with bisantrene initiated Dec 1991
- Mucositis complication on Dec 1991; treated with acyclovir and morphine derivatives
- Discharged Dec 1991
- Myelograms on Dec 1991, and Jan 1992, showed nonblastic aplasia and nonblastic poor marrow, respectively. Aplasia ended on Jan 1992, with 600 PN and 140,000 platelets, which considered complete remission
- Autologous bone marrow transplantation Feb 1992 after conditioning treatment, including fractionated irradiation 12 Gy x 6 sessions with lung protection at 9 Gy + cyclophosphamide 60 mg/kg/day for 2 days
- Discharged from hospital on Day 60 (Apr 1992) with persistence of platelet transfusions
- Thrombopenia was corrected (>50,000) starting Jul 1992
- Normal complete blood count reached in Nov 1992 with normal cardiac ultrasound

Notable medical history since last cancer visit

- Post-transfusion hepatitis C
- Delivered infant, Jun 2015

OUTCOME: The patient is alive today and the mother of one child born in June 2015

FIGURE 2. Patient A treatment lines and milestones.



CASE REPORT

CASE 2. Patient S

Born: Jan 1977
Sex: Female

AML diagnosis date: Jan 1984 (Figure 3)

- Diagnosed with AML type M3
- Protocol LAP84
  - Total daunorubicin dose: 500 mg/m² including induction + 3 consolidation cycles
- Complete remission Feb 8, 1984
- Maintenance treatment initiated May 1984

Relapse date: Nov 1984

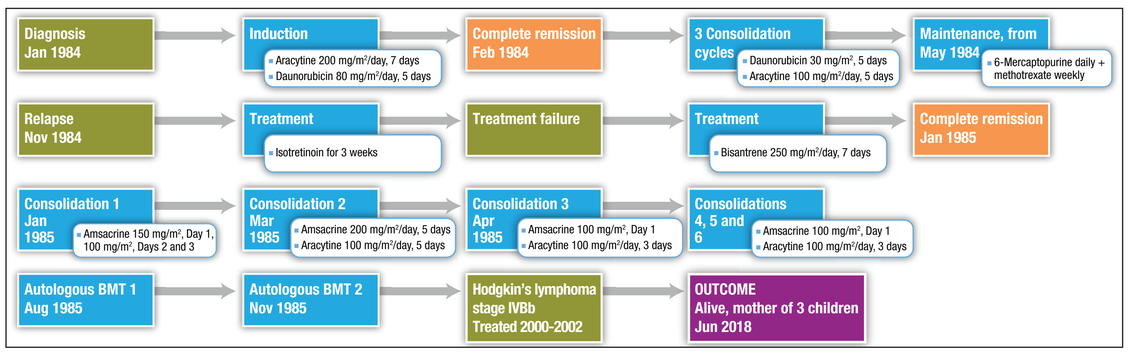
- Treatment with isotretinoin for 3 weeks failed; myelogram on Dec 1984, showed 93% blasts
- Bisantrene treatment initated on Dec 1984
  - Allergic reaction on Day 1 linked to a fast infusion rhythm: hives, abdominal pain, pain in the forearms, fever, headache. Similar allergic symptoms occurred on Day 2 despite a slow infusion rhythm. Allergic symptoms treated with polaramine and hydrocortisone
- Other adverse events:
  - Disseminated intravascular coagulation treated with heparin therapy and platelet transfusions
  - Diarrhea
  - Mucositis
  - Aplasia with febrile neutropenia
- Myelograms
  - Dec 1984: poor bone marrow without blasts or megakaryocytes
  - Jan 1985: poor bone marrow with 8% blasts and beginning of regeneration
  - Jan 1985: 3% blasts, 45% granulocytes, 10% monocytes, 10% erythroblasts with megakaryocytes, and 30% lymphocytes, which was considered a complete remission profile
- Aplasia ended on Jan 1985, with a WBC of 2800 with 35% neutrophils, 14% monocytes, and 151,000 platelets
- First consolidation cycle, Jan 1985; complicated with febrile neutropenia
- Myelogram on Feb 1985: no blasts, 27% granulocytes, 18% monocytes, 4% erythroblasts, megakaryocytes present, 51% lymphocytes
- Second through sixth consolidation cycles, Mar 1985 – Jul 1985
  - Total dose of amsacrine: 750 mg/m²
- Myelograms on Mar 1985, and Jun 1985, were normal as was the cardiac ultrasound done in May 1985
- First autologous bone marrow transplantation, Aug 1985 (marrow taken on Aug 1985) after conditioning treatment with melphalan 140 mg/m²
- Second autologous bone marrow transplantation on Nov 1985 (marrow taken on Nov 1985) after same conditioning treatment; treated with Asta-Z
- Positive LAV serology found after second bone marrow transplantation tests

Notable medical history since last AML visit

- Treatment of post-transfusion HIV infection, starting Sep 1997
- Thyroidectomy for multinodular goiter, Mar 1998
- In 2000, diagnosed with nodular Hodgkin's lymphoma stage IVBb, affecting bones and the cervical mediastinal, axillary and hilar regions as shown by fluorodeoxyglucose positron emission tomography (FDG PET); treated with 2 cycles of doxorubicin-bleomycin-vinblastine (ABV) and 2 cycles of cyclophosphamide-vincristine-procarbazine-prednisone (COPP); Aug 2001 FDG PET scan normal; patient received 5 cycles of COPP and vinorelbine every 2 weeks + procarbazine 1 week/month until May 2002; total 12 vinorelbine injections

OUTCOME: The patient is alive today and the mother of 3 children

FIGURE 3. Patient S treatment lines and milestones.



CONCLUSIONS

- Bisantrene is therapeutically active, with a unique safety profile that maybe particularly appropriate for the treatment of pediatric r/r AML.
- Published efficacy results from prior salvage studies of bisantrene in adult and pediatric AML and the long-term case reports presented here support a renewed interest in clinical development of bisantrene.

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