Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

December 2014 Volume 12, Issue 12, Supplement 20

Advances in the Treatment of Relapsed/Refractory Acute Lymphoblastic Leukemia: A Case Study Compendium

Faculty

Gail J. Roboz, MD
Associate Professor of Medicine
Director, Leukemia Program
New York-Presbyterian Hospital
Weill Cornell Medical Center
New York, New York

Elias J. Jabbour, MD
Associate Professor
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Stefan Faderl, MD
Chief, Leukemia Division
John Theurer Cancer Center
at Hackensack University Medical Center
Hackensack, New Jersey

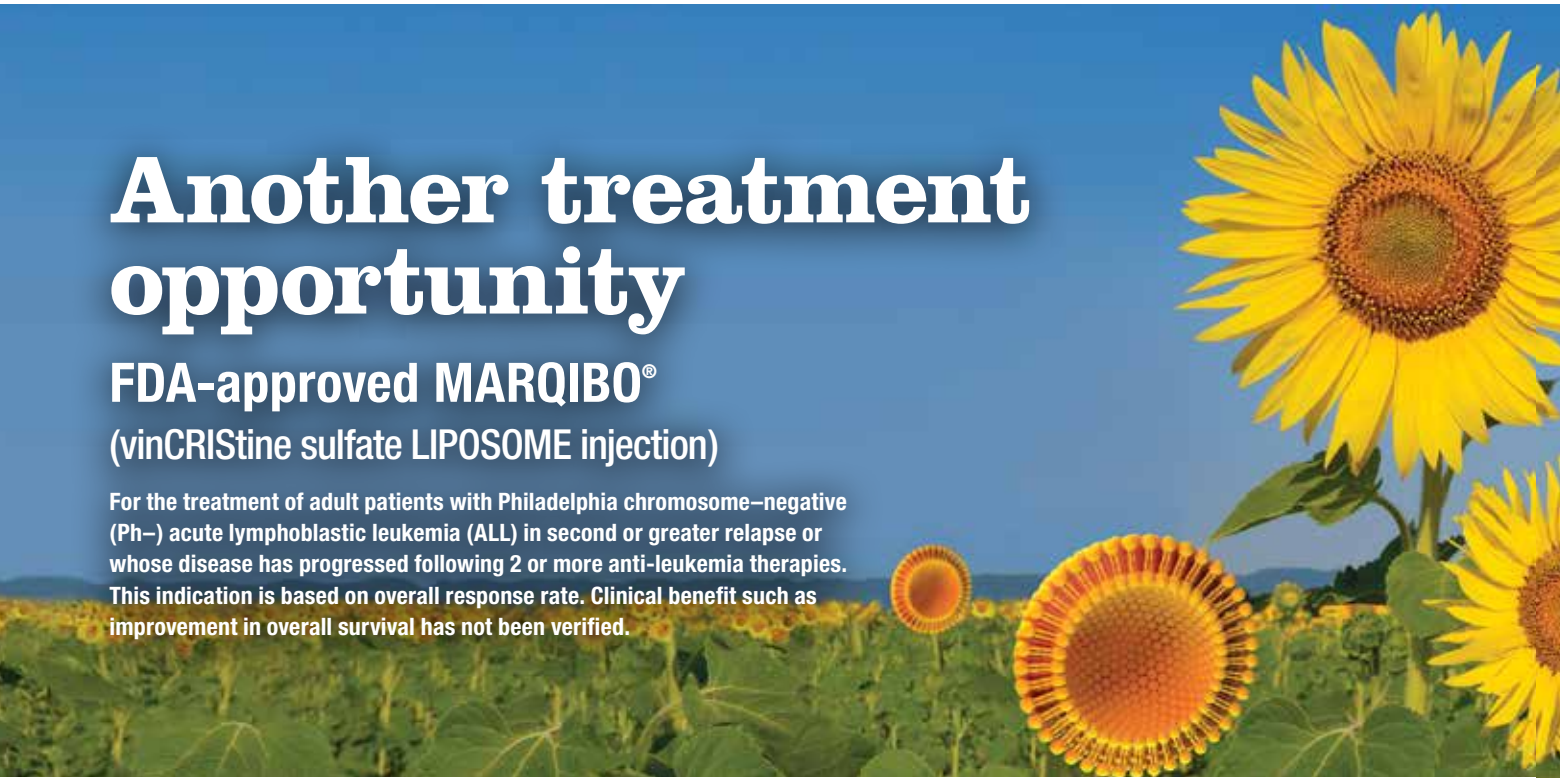
With an introduction by:

Dan Douer, MD
Attending Physician
Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

Abstract: Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by proliferation of immature lymphoid cells throughout the bone marrow and peripheral blood. Most cases are diagnosed before the age of 20 years. Adults have a worse prognosis than children. Approximately half of adult ALL patients relapse after their initial treatment. There is no standard treatment for ALL; strategies vary according to the patient's age, comorbidities, and Philadelphia chromosome status. Regimens used in pediatric patients are being adapted for use in adults. Frontline management can include hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine (hyper-CVAD) and the Berlin-Frankfurt-Münster regimen. Relapsed/refractory patients have several options, including a regimen consisting of fludarabine, high-dose cytarabine, and granulocyte colony–stimulating factor (FLAG); tyrosine kinase inhibitors; and chemotherapy. The US Food and Drug Administration recently approved 3 therapies for these patients: clofarabine, nelarabine, and vincristine sulfate liposome injection, a modified formulation of vincristine that allows the drug to be administered at a higher dosage. Several novel strategies are currently under investigation, including the monoclonal antibody blinatumomab, a bispecific T-cell engager that targets the B-cell–specific antigen CD19 and activates T cells to exert cytotoxic activity against the target B cell. This clinical roundtable monograph features case studies that illustrate important points in the management of adult patients with relapsed/refractory ALL.

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE



Another treatment opportunity

FDA-approved MARQIBO®

(vinCRIStine sulfate LIPOSOME injection)

For the treatment of adult patients with Philadelphia chromosome–negative (Ph–) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following 2 or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.

- **15.4% (10/65) overall response rate in patients who received multiple prior therapies (4.6% CR + 10.8% CRi) (95% CI 7.6–26.5)[1]**
  - 100% had previously received non-liposomal (standard) vincristine
  - 48% had undergone prior hematopoietic stem cell transplant (HSCT)
  - 51% had received 3 or more prior therapies
  - 45% were refractory to their immediate prior therapy
  - 85% had precursor B-cell ALL and 15% had precursor T-cell ALL
  - 100% were ineligible for immediate HSCT at enrollment
  - 34% had not received asparaginase products
- **Median duration of CR or CRi[1]**
  - 28 days (95% CI 7, 36) based on the first date of CR or CRi to the date of the last available histologic assessment of the same response (n=8)
  - 56 days (95% CI 9, 65) based on the first date of CR or CRi to the date of documented relapse, death, or subsequent chemotherapies, including HSCT (n=10)
- **MARQIBO is sphingomyelin/cholesterol-based liposome–encapsulated vincristine[1]**
  - Plasma clearance of MARQIBO is slow, 345 mL/h, at a dose of 2.25 mg/m^2. This is in comparison to the rapid clearance of non-liposomal vincristine sulfate at 189 mL/min/m^2 (11,340 mL/h)
  - Slow clearance of MARQIBO contributes to a much higher area under the curve (AUC) for MARQIBO relative to non-liposomal vincristine sulfate
- **The recommended dose of MARQIBO is 2.25 mg/m^2 intravenously over 1 hour every 7 days.[1] A dose of MARQIBO is calculated based on the patient's actual body surface area**

Important Safety Information

WARNING

- **For Intravenous Use Only—Fatal if Given by Other Routes**
- **Death has occurred with intrathecal administration**
- **MARQIBO (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage**

Contraindications

- MARQIBO is contraindicated in patients with demyelinating conditions, including Charcot-Marie-Tooth syndrome; in patients with hypersensitivity to vincristine sulfate or any of the other components of MARQIBO; and for intrathecal administration

SPECTRUM™ PHARMACEUTICALS
and its wholly-owned subsidiary TALON® THERAPEUTICS

www.sppirx.com

Warnings and Precautions

- MARQIBO is for intravenous use only—fatal if given by other routes. Intrathecal use is fatal
- Extravasation causes tissue injury. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures
- Sensory and motor neuropathy are common and cumulative. Monitor patients for peripheral motor and sensory, central and autonomic neuropathy and reduce, interrupt, or discontinue dosing. Patients with preexisting severe neuropathy should be treated with MARQIBO only after careful risk-benefit assessment
- Neutropenia, thrombocytopenia, or anemia may occur. Monitor blood counts prior to each dose. Consider dose modification or reduction as well as supportive care measures if Grade 3 or 4 myelosuppression develops
- Anticipate, monitor for, and manage tumor lysis syndrome
- A prophylactic bowel regimen should be instituted with MARQIBO to prevent constipation, bowel obstruction, and/or paralytic ileus
- Severe fatigue can occur requiring dose delay, reduction, or discontinuation of MARQIBO
- Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred. Monitor liver function and modify or interrupt dosing for hepatic toxicity
- MARQIBO can cause fetal harm. Advise women of potential risk to fetus

Adverse Events

- The most commonly reported adverse reactions (incidence >30%) in clinical studies include constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%)
- A total of 75.9% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included febrile neutropenia (20.5%), pyrexia (13.3%), hypotension (7.2%), respiratory distress (6.0%), and cardiac arrest (6.0%)
- Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The most common adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%)
- Deaths occurred in 23% of patients in study 1. The nonleukemia-related causes of death were brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multisystem organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1)

Drug Interactions

- MARQIBO is expected to interact with drugs known to interact with non-liposomal vincristine sulfate, therefore the concomitant use of strong CYP3A inhibitors or the use of potent P-glycoprotein inhibitors or inducers should be avoided

Use in Specific Populations

- The safety and effectiveness of MARQIBO in pediatric patients have not been established
- It is not known whether MARQIBO is excreted in human milk

Please see Brief Summary of Prescribing Information, including the BOXED WARNINGS, for MARQIBO on adjacent pages. Please see Prescribing Information at MARQIBO.com.

1. MARQIBO [prescribing information]. October 2012.

Marqibo®

(vinCRIStine sulfate LIPOSOME injection)

for intravenous infusion

Consider the Opportunity

Marqibo® (vinCRIStine sulfate LIPOSOME injection) BRIEF SUMMARY
Please see the Marqibo package insert for full Prescribing Information.

WARNING

- **For Intravenous Use Only—Fatal if Given by Other Routes.**
- **Death has occurred with intrathecal administration.**
- **Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vinCRIStine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.**

INDICATIONS AND USAGE

Adult ALL in Second or Greater Relapse

Marqibo® is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.

DOSAGE AND ADMINISTRATION

For Intravenous Use Only—Fatal if Given by Other Routes.

Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.

Recommended Dosage

The recommended dose of Marqibo is 2.25 mg/m^2 intravenously over 1 hour once every 7 days. Marqibo is liposome-encapsulated vincristine.

Dose Modifications: Peripheral Neuropathy

Marqibo is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome [*see Contraindications*]. Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment [*see Warnings and Precautions*]. For dose or schedule modifications guidelines for patients who experience peripheral neuropathy, see Table 1.

Table 1. Recommended Dose Modifications for Marqibo-related Peripheral Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
If the patient develops Grade 3 (severe symptoms; limiting self-care activities of daily living [ADL][b]) or persistent Grade 2 (moderate symptoms; limiting instrumental ADL[c]) peripheral neuropathy:	Interrupt Marqibo. If the peripheral neuropathy remains at Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1 or 2, reduce the Marqibo dose to 2 mg/m^2.
If the patient has persistent Grade 2 peripheral neuropathy after the first dose reduction to 2 mg/m^2:	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1, reduce the Marqibo dose to 1.825 mg/m^2.
If the patient has persistent Grade 2 peripheral neuropathy after the second dose reduction to 1.825 mg/m^2:	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the toxicity recovers to Grade 1, reduce the Marqibo dose to 1.5 mg/m^2.

[a] Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
[b] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
[c] Instrumental ADL: refers to preparing meals, shopping for groceries and clothes, using telephone, managing money, etc.

Preparation and Handling

Items Required by the Pharmacy to Prepare Marqibo

- Marqibo Kit
- Water bath[a]
- Calibrated thermometer[a] (0°C to 100°C)
- Calibrated electronic timer[a]
- Sterile venting needle or other suitable device equipped with a sterile 0.2 micron filter
- 1 mL or 3 mL sterile syringe with needle, and
- 5 mL sterile syringe with needle.

[a] The manufacturer will provide the water bath, calibrated thermometer, and calibrated electronic timer to the medical facility at the initial order of Marqibo and will replace them every 2 years.

Preparation Instructions for Marqibo (vinCRIStine sulfate LIPOSOME injection), 5 mg/31 mL (0.16 mg/mL)

Procedures for handling and disposal of anticancer drugs should be followed [*see References*]. Call [1 888 292 9617] if you have questions about the preparation of Marqibo. Marqibo takes approximately 60 to 90 minutes to prepare. The preparer should have dedicated uninterrupted time to prepare Marqibo due to the extensive monitoring of temperature and time required for the preparation.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Marqibo. The preparation steps of Marqibo that involve mixing the Sodium Phosphate Injection, Sphingomyelin/Cholesterol Liposome Injection, and VinCRIStine Sulfate Injection must be done in a biological safety cabinet or by established pharmacy safety procedures for the preparation of sterile injectable formulations and hazardous drugs. However, the preparation steps that involve placement of the vial in the water bath must be done outside of the sterile area.

Do not use with in-line filters. Do not mix with other drugs.

1. Fill a water bath with water to a level of at least 8 cm (3.2 inches) measured from the bottom and maintain this minimum water level throughout the procedure. The water bath must remain outside of the sterile area.
2. Place a calibrated thermometer in the water bath to monitor water temperature and leave it in the water bath until the procedure has been completed.
3. Preheat water bath to 63°C to 67°C. Maintain this water temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the Marqibo Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2 micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRIStine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.
9. Withdraw 5 mL of VinCRIStine Sulfate Injection.
10. Inject 5 mL of VinCRIStine Sulfate Injection into the Sodium Phosphate Injection vial.
11. Remove the venting needle and gently invert the Sodium Phosphate Injection vial 5 times to mix. DO NOT SHAKE.
12. Fit Flotation Ring around the neck of the Sodium Phosphate Injection vial.
13. Confirm that the water bath temperature is at 63°C to 67°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRIStine Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and place into the water bath for 10 minutes using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 63°C to 67°C.
14. IMMEDIATELY after placing the Sodium Phosphate Injection vial into the water bath, record the constitution start time and water temperature on the Marqibo Overlabel.
15. At the end of the 10 minutes, confirm that the water temperature is 63°C to 67°C using the calibrated thermometer. Remove the vial from the water bath (use tongs to prevent burns) and remove the Flotation Ring.
16. Record the final constitution time and the water temperature on the Marqibo Overlabel.
17. Dry the exterior of the Sodium Phosphate Injection vial with a clean paper towel, affix Marqibo (vinCRIStine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. DO NOT SHAKE.
18. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
19. Marqibo (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. ONCE PREPARED, STORE AT CONTROLLED ROOM TEMPERATURE (15°C to 30°C, 59°F to 86°F) FOR NO MORE THAN 12 HOURS.
20. Swab the top of the vial now containing Marqibo with a sterile alcohol pad and return the vial back into the biological safety cabinet.
21. Calculate the patient's Marqibo dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo dose from an infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
22. Inject the dose of Marqibo into the infusion bag to result in a final volume of 100 mL.
23. Complete the information required on the Infusion Bag Label and apply to the infusion bag.
24. Finish administration of the diluted product within 12 hours of the initiation of Marqibo preparation.
25. Empty, clean, and dry the water bath after each use.
26. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

CONTRAINDICATIONS

Marqibo is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome.

Marqibo is contraindicated in patients with hypersensitivity to vincristine sulfate or any of the other components of Marqibo (vinCRIStine sulfate LIPOSOME injection).

Marqibo is contraindicated for intrathecal administration.

WARNINGS AND PRECAUTIONS

For Intravenous Use Only

Fatal if Given by Other Routes. Death has occurred with intrathecal use.

Extravasation Tissue Injury

Only administer through a secure and free-flowing venous access line. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures.

Neurologic Toxicity

Sensory and motor neuropathies are common and are cumulative. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment. Orthostatic hypotension may occur. The risk of neurologic toxicity is greater if Marqibo is administered to patients with preexisting neuromuscular disorders or when other drugs with risk of neurologic toxicity are being given. In the studies of relapsed and/or refractory adult ALL patients, Grade ≥3 neuropathy events occurred in 32.5% of patients. Worsening neuropathy requires dose delay, reduction, or discontinuation of Marqibo [*see Dosage and Administration*].

Myelosuppression

Monitor complete blood counts prior to each dose of Marqibo. If Grade 3 or 4 neutropenia, thrombocytopenia, or anemia develops, consider Marqibo dose modification or reduction as well as supportive care measures.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients with ALL receiving Marqibo.

Anticipate, monitor for, and manage.

Constipation and Bowel Obstruction

Ileus, bowel obstruction, and colonic pseudo-obstruction have occurred. Marqibo can cause constipation [*see Adverse Reactions*]. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction, and/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners, such as docusate. Additional treatments, such as senna, bisacodyl, milk of magnesia, magnesium citrate, and lactulose may be considered.

Fatigue

Marqibo can cause severe fatigue. Marqibo dose delay, reduction, or discontinuation may be necessary.

Hepatic Toxicity

Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred. Elevated levels of aspartate aminotransferase of Grade ≥3 occurred in 6-11% of patients in clinical trials. Monitor hepatic function tests. Reduce or interrupt Marqibo for hepatic toxicity.

Embryofetal Toxicity

Marqibo can cause fetal harm when administered to a pregnant woman. Vincristine sulfate liposome injection was teratogenic or caused embryo-fetal death in animals.

Women of childbearing potential should avoid becoming pregnant while being treated with Marqibo. There are no adequate and well-controlled studies of Marqibo in pregnant women and there were no reports of pregnancy in any of the clinical studies in the Marqibo clinical development program. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations*].

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- For intravenous use only [*see Warnings and Precautions*]
- Extravasation tissue injury [*see Warnings and Precautions*]
- Peripheral Neuropathy [*see Warnings and Precautions*]
- Myelosuppression [*see Warnings and Precautions*]
- Tumor lysis syndrome [*see Warnings and Precautions*]
- Constipation and bowel obstruction [*see Warnings and Precautions*]
- Fatigue [*see Warnings and Precautions*]
- Hepatic toxicity [*see Warnings and Precautions*]

Clinical Trials Safety Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Integrated Summary of Safety in Relapsed and/or Refractory Ph- Adult Acute Lymphoblastic Leukemia

Marqibo, at a dose of 2.25 mg/m^2 weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. Adverse reactions were observed in 100% of patients. The most common adverse reactions (>30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%)

Adverse reactions of Grade 3 or greater were reported in 96% of patients.

Adverse reactions of Grade 3 or greater and occurring in ≥5% of patients are summarized in Table 2.

Table 2. Most Commonly Reported (>5%) Grade[a] 3 or Greater Adverse Reactions among 83 Patients Receiving the Clinical Dosing Regimen

Adverse Reactions ≥3	Study 1 and 2 (N=83) n (%)
Blood and Lymphatic System Disorders	*47 (56.6)*
Febrile Neutropenia	26 (31.3)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
Infections	*33 (39.8)*
Pneumonia	7 (8.4)
Septic Shock	5 (6.0)
Staphylococcal Bacteremia	5 (6.0)
Neuropathy[b]	*27 (32.5)*
Peripheral Sensory and Motor Neuropathy	14 (16.7)
Constipation	4 (4.8)
Ileus, Colonic Pseudo-Obstruction	5 (6.0)
Asthenia	4 (4.8)
Muscular Weakness	1 (1.2)
Respiratory Thoracic and Mediastinal Disorders	*17 (20.5)*
Respiratory Distress	5 (6.0)
Respiratory Failure	4 (4.8)
General Disorders and Administration Site Condition	*31 (37.3)*
Pyrexia	12 (14.5)
Fatigue	10 (12.0)
Pain	7 (8.4)
Gastrointestinal Disorders	*21 (25.3)*
Abdominal Pain	7 (8.4)
Investigations	*20 (24.1)*
Aspartate Aminotransferase Increased	6 (7.2)
Vascular Disorders	*8 (9.6)*
Hypotension	5 (6.0)
Psychiatric Disorders	*9 (10.8)*
Mental Status Changes	3 (3.6)
Cardiac Disorders	*9 (10.8)*
Cardiac Arrest	5 (6.0)
Renal and Urinary Disorders	*6 (7.2)*
Musculoskeletal and Connective Tissue Disorders	*7 (8.4)*

[a] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
[b] Including neuropathy-associated adverse reactions.

A total of 75.9% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included febrile neutropenia (20.5%), pyrexia (13.3%), hypotension (7.2%), respiratory distress (6.0%), and cardiac arrest (6.0%).

Dose reduction, delay, or omission occurred in 53% of patients during the treatment.

Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The most common adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%).

Adverse reactions related to neuropathy and leading to treatment discontinuation were decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain, each reported in at least 1 patient.

Deaths occurred in 23% of patients in study 1. The nonleukemia-related causes of deaths were brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multi system organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1).

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Marqibo. Marqibo is expected to interact with drugs known to interact with non-liposomal vincristine sulfate.

Simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included non-liposomal vincristine sulfate have been reported to reduce blood levels of phenytoin and to increase seizure activity.

CYP3A Interactions

Vincristine sulfate, the active agent in Marqibo, is a substrate for cytochrome P450 3A isozymes (CYP3A); therefore, the concomitant use of strong CYP3A inhibitors should be avoided (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin). Similarly, the concomitant use of strong CYP3A inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort).

P-glycoprotein Interactions

Vincristine sulfate, the active agent in Marqibo, is also a substrate for P-glycoprotein (P-gp). The effect of concomitant use of potent P-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo. Therefore the concomitant use of potent P-gp inhibitors or inducers should be avoided.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D [*see Warnings and Precautions*]

Based on its mechanism of action and findings from animal studies, Marqibo can cause fetal harm when administered to pregnant women.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. In an embryofetal developmental study, pregnant rats were administered vincristine sulfate liposome injection intravenously during the period of organogenesis at vincristine sulfate doses of 0.022 to 0.09 mg/kg/day. Drug-related adverse effects included fetal malformations (skeletal and visceral), decreases in fetal weights, increased numbers of early resorptions and post-implantation losses, and decreased maternal body weights. Malformations were observed at doses ≥0.044 mg/kg/day in animals at systemic exposures approximately 20-40% of those reported in patients at the recommended dose.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Marqibo in pediatric patients have not been established.

Geriatric Use

Safety and effectiveness in elderly individuals have not been established. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

The influence of renal impairment on the safety, efficacy, and pharmacokinetics of Marqibo has not been evaluated.

Hepatic Impairment

Non-liposomal vincristine sulfate is excreted primarily by the liver. The influence of severe hepatic impairment on the safety and efficacy of Marqibo has not been evaluated.

The pharmacokinetics of Marqibo was evaluated in patients with moderate hepatic dysfunction (Child-Pugh B) secondary to melanoma liver metastases. The dose-adjusted maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of Marqibo in patients with moderate hepatic impairment was comparable to the C_{max} and AUC of patients with ALL who had otherwise normal hepatic function.

OVERDOSAGE

When Marqibo (vinCRIStine sulfate LIPOSOME injection) was administered at a dose of 2.4 mg/m^2, severe toxicities including motor neuropathy of Grade 3, grand mal seizure of Grade 4, and elevated aspartate aminotransferase and hyperbilirubinemia of Grade 4 were reported in 1 patient each. There is no known antidote for overdosage.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with Marqibo or non-liposomal vincristine sulfate. Based on the mechanism of action and genotoxicity findings in nonclinical studies conducted with non-liposomal vincristine sulfate, Marqibo may be carcinogenic.

No genotoxicity studies have been conducted with Marqibo. Non-liposomal vincristine was genotoxic in some *in vitro* and *in vivo* studies.

The single- and repeat-dose animal toxicology study results indicate that Marqibo can impair male fertility, consistent with the literature on non-liposomal vincristine sulfate. Administration of vincristine liposome injection causes testicular degeneration and atrophy, and epididymal aspermia in rats.

Gonadal dysfunction has been reported in both male and female post-pubertal patients who received multi-agent chemotherapy including non-liposomal vincristine sulfate.

The degree to which testicular or ovarian functions are affected is age-, dose-, and agent-dependent. Recovery may occur in some but not all patients.

Animal Toxicology and/or Pharmacology

In a repeat-dose comparative toxicology study in rats, vincristine sulfate liposome injection or non-liposomal vincristine sulfate was administered to animals intravenously once per week for 6 weeks. Clinical signs of toxicity consistent with neurotoxicity were greater with vincristine sulfate liposome injection than with non-liposomal vincristine sulfate at equal vincristine sulfate doses of 2 mg/m^2/week and included uncoordinated movements, weakness, reduced muscle tone, and limited usage of the limbs. Neurological testing indicated drug-induced peripheral neurotoxicity with both drugs. Based on the histopathology examination after 6 weekly doses, vincristine sulfate liposome injection induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of non-liposomal vincristine sulfate. In a separate tissue distribution study in rats, administration of 2 mg/m^2 of intravenous liposomal or non-liposomal vincristine sulfate showed greater accumulation of vincristine sulfate in sciatic and tibial nerves (as well as the lymph nodes, spleen, and bone marrow) of the animals following vincristine sulfate liposome injection.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following with patients prior to treatment with Marqibo:

Extravasation Tissue Injury: Advise patients to report immediately any burning or local irritation during or after the infusion [*see Warnings and Precautions*].

Ability to Drive or Operate Machinery or Impairment of Mental Ability: Marqibo may cause fatigue and symptoms of peripheral neuropathy. Advise patients not to drive or operate machinery if they experience any of these symptoms [*see Warnings and Precautions*].

Gastrointestinal/Constipation: Patients receiving Marqibo may experience constipation. Advise patients how to avoid constipation by a diet high in bulk fiber, fruits and vegetables, and adequate fluid intake as well as use of a stool softener, such as docusate. Instruct patients to seek medical advice if they experience symptoms of constipation such bowel movement infrequency, abdominal pain, bloating, diarrhea, nausea, or vomiting [*see Warnings and Precautions*].

Pregnancy/Nursing: Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with Marqibo [*see Warnings and Precautions*]. Instruct patients to report pregnancy to their physicians immediately. Advise patients that they should not receive Marqibo while pregnant or breastfeeding. If a patient wishes to re-start breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician [*see Use in Specific Populations*].

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking [*see Drug Interactions*].

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the feet or hands [*see Warnings and Precautions*].

Other: Instruct patients to notify their physicians if they experience fever, productive cough, or decreased appetite [*see Warnings and Precautions*].

REFERENCES

1. NIOSH Alert: Preventing occupational exposure to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* (2006) 63:1172-1193.
4. Polovich M, White JM, Kelleher LO (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

Distributed by:

Spectrum Pharmaceuticals, Inc. and its wholly-owned subsidiary Talon Therapeutics, Inc., 11500 South Eastern Ave., Suite 240, Henderson, NV 89052

0125-080401

www.sppirx.com

Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Advances in the Treatment of Relapsed/Refractory ALL: Introduction to a Case Study Compendium

Dan Douer, MD
Attending Physician, Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by the proliferation of immature lymphoid cells throughout the bone marrow and peripheral blood. More than half of ALL patients are diagnosed before the age of 20 years.[1,2] In children with ALL, 5-year overall survival rates have risen from 83.7% in 1990 through 1994 to 90.4% in 2000 through 2005.[3] Adults with ALL have worse 5-year overall survival rates, at 24.1% for those ages 40 to 59 years and 17.7% for those ages 60 to 69 years.[4]

Management of ALL

The treatment landscape of ALL is changing. Management approaches will vary according to whether patients have the Philadelphia (Ph) chromosome. Among patients with Ph-positive disease, the use of tyrosine kinase inhibitors, including dasatinib or imatinib, significantly improves overall outcome. The following discussion will focus on Ph-positive ALL.

Frontline Treatment

There is no standard frontline treatment for adult ALL patients. During the 1990s, the treatment of adult ALL evolved (with a few exceptions) in 2 fundamentally different directions that both provided a higher complete response rate of approximately 90%.[5] In community settings, patients often receive treatment with the hyper-CVAD regimen, which includes cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine.[6,7] The other regimen, which was originally developed in children and adjusted for adults, is the Berlin-Frankfurt-Münster (BFM) model (and its variants).[8-13] With both approaches, the long-term survival is 35% to 40%. Although hyper-CVAD has no proven advantage, its common use in the United States is most likely attributable to a much simpler delivery structure than the BFM regimen.

More recently, other frontline treatment approaches have been studied, mostly in young adults. These regimens are based on pediatric protocols, reflecting the improved outcomes observed among children with ALL compared with adults. Such pediatric and "pediatric-inspired" regimens, which incorporate increased doses of asparaginase, have improved overall survival from 40% to 65% in adults.[14-19]

One of the more complicated questions surrounding ALL treatment concerns patients older than 40 years. It is possible that some of these patients, especially those in good health, can benefit from pediatric-based protocols. However, this option is not included in guidelines, such as those from the National Comprehensive Cancer Network.[20]

Relapsed ALL

Approximately half of adult ALL patients relapse after their initial treatment.[21] After the disease relapses, the goal of therapy is to coax the patient into a remission that will last for at least a few weeks so that a bone marrow transplant—the only curative approach—can be performed. Many patients never go on to receive a transplant for a multitude of reasons, such as they were too sick, they never

achieved an adequate remission, or their remission was too short before they relapsed.[22] Overall, response rates for the second remission approach only 25% to 50%, depending on the duration of the first remission.[23-27]

There is no standard treatment recommended for induction therapy after relapse.[28] Overall, no one regimen is profoundly better than the others. Only 30% to 60% of patients will respond, and those responses are usually of a short duration.[23]

One popular strategy for salvage therapy consists of fludarabine, high-dose cytarabine, and granulocyte colony–stimulating factor (FLAG). Although this regimen was originally created for AML, it has been adopted for relapsed ALL.[29,30] A modification of this regimen containing idarubicin has shown activity in relapsed and refractory ALL.[31] Another strategy for salvage therapy of ALL is a BFM regimen, which was originally developed for pediatric patients, and modified with reduced dosages for adults.[13] The BFM strategy includes high-dose methotrexate and cytarabine in a small study of 19 patients; the response rate was 60%, and all but 1 patient experienced a relapse of disease, further demonstrating the difficulty in achieving and maintaining a second remission.[24]

Three chemotherapy drugs were recently approved by the US Food and Drug Administration (FDA). Clofarabine is a nucleoside analogue that is approved as a single agent for use in patients ages 21 years and younger. It is often used off-label in adults, although at a lower dose of 40 mg/m^2. In heavily pretreated pediatric patients, single-agent clofarabine is associated with a response rate of approximately 20%.[32] Another drug is the nucleoside analogue nelarabine, which has been evaluated in adults with relapsed/refractory T-cell ALL or T-cell lymphoblastic leukemia. The rate of complete hematologic remission (including patients with incomplete blood count recovery) was 31%.[33] The median disease-free survival was 20 weeks, and the 1-year overall survival was 28%. Nelarabine is frequently associated with neurologic toxicity, but administering it on an every-other-day schedule for 3 doses substantially decreases this adverse event.

Vincristine sulfate liposome injection is a modified formulation of vincristine, a drug commonly used in ALL. Traditional vincristine is associated with severe peripheral neuropathy; as a result, it is typically underdosed when given to patients. Vincristine sulfate liposome injection is a sphingomyelin- and cholesterol-based nanoparticle formulation of vincristine, which was designed to overcome the dosing and pharmacokinetic limitations of standard vincristine. Vincristine sulfate liposome injection exhibits slower systemic release and better penetration into organs and the bone marrow.[34-36] As a result, a higher dose of 2.25 mg/m^2 can be administered. In a phase 2 trial of 65 patients with Ph-negative ALL in second or greater relapse who received single-agent vincristine sulfate liposome injection, the response rate was 35%, with a 20% rate of complete response/complete response with incomplete hematologic recovery.[37] The duration of this response was 23 weeks, and several patients were able to successfully bridge to bone marrow transplant. The median overall survival of all patients was 4.6 months; among those who achieved a complete response/complete response with incomplete hematologic recovery, the median survival was 7.7 months (Figure 1). Vincristine sulfate liposome injection is approved in second-line or later treatment of ALL, but it can also be used off-label in the frontline setting. It requires only once-weekly dosing—making it attractive for the community setting—and it does not suppress the bone marrow. The primary toxicities associated with its use include peripheral neuropathy and constipation, but the frequency of these adverse events is not higher than what is observed with standard vincristine, despite the increased dosage given. Vincristine sulfate liposome injection is currently approved as a single agent. It remains unclear whether substituting standard vincristine with vincristine sulfate liposome injection in a combination regimen, such as hyper-CVAD, will be beneficial.

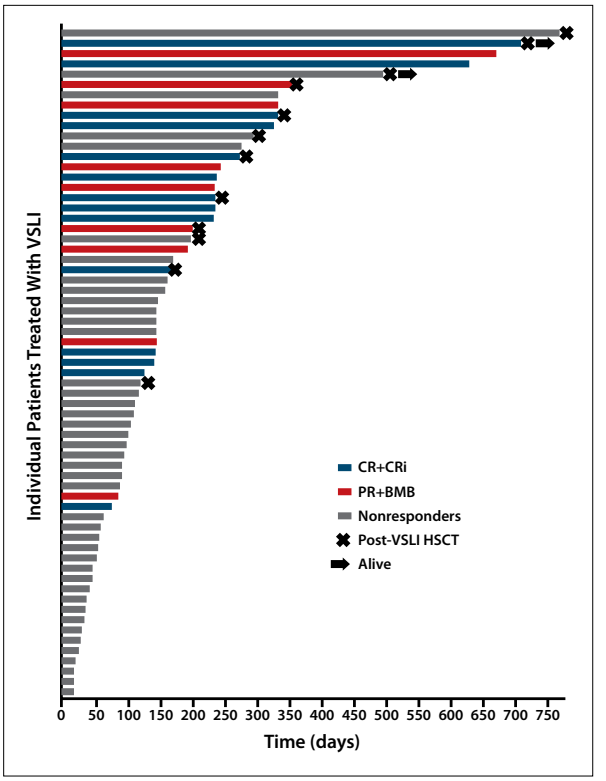


Figure 1. Overall survival and HSCT among patients treated with VSLI in a phase 2 trial. BMB, bone marrow blast response; CR, complete response; CRi, complete response with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; PR, partial remission; VSLI, vincristine sulfate liposome injection. Adapted from O'Brien S et al. *J Clin Oncol.* 2013;31(6):676-683.[37]

Investigational Agents for Relapsed ALL

A primary focus for the future of ALL treatment development is immunotherapy. Blinatumomab is a member of a novel class of agents, the bispecific T-cell engagers (BiTEs).[38] It is a monoclonal antibody constructed to target the malignant B-cell–specific CD19 antigen as well as the normal T-cell–specific CD3 molecule. By binding to these 2 cell types, blinatumomab promotes T-cell activation against the ALL cell. In a small study of 18 patients with relapsed/refractory ALL, blinatumomab was associated with a high rate of complete remission (67%), which included several rapid responses that were negative for minimal residual disease.[39] In a confirmatory, open-label, single-arm, multicenter, phase 2 study, blinatumomab was evaluated in 189 patients with relapsed/refractory ALL (median age, 39 years).[40] This study reported that 43% of patients achieved a complete remission with a full or partial hematologic recovery. These responses were rapid, with 80% occurring during the first treatment cycle. The primary drawback of blinatumomab appears to be its short duration of remission, which is approximately 6 months. The administration of blinatumomab poses logistic challenges, as it must be given intravenously as a 24-hour infusion over 28 days per cycle, and in the United States, the bag must be changed no later than 48 hours.

A second strategy under clinical development in ALL is chimeric antigen receptor (CAR) T-cell immunotherapy. With this strategy, T cells are harvested from the patient and then genetically engineered to express a CAR specific for CD19. The cells are also modified to contain a viral vector that induces T-cell expansion and proliferation after the antigen is recognized. After they are expanded ex vivo, the modified T cells are then infused back into the patient. The average remission rate for CAR T-cell immunotherapy in ALL is 88%, which is very high in comparison with other salvage therapies.[41] CAR T cells hold great promise for the treatment of relapsed/refractory ALL, as this therapy has achieved significantly prolonged overall survival as compared with current regimens.[42,43] The primary drawback associated with CAR T-cell immunotherapy is its potential for toxicity. The 2 main toxicities seen with CAR T cells are cytokine release syndrome (manifested by fevers, chills, hypertension, and hypoxia) and encephalopathy (manifested by seizures and decreased or altered mental status). Both of these toxicities can be severe, but they can be ameliorated by treatment with an anti-interleukin 6 agent or steroids. (Steroids, however, can also block the action of the CAR T cells and thereby reduce their efficacy.)

Antibody-drug conjugates are also under investigation in relapsed/refractory ALL. These agents consist of an antibody directed against a relevant ALL antigen, which is used to target the molecule to an ALL cell. The antibody is bound to a drug that is cytotoxic to the ALL cell. Inotuzumab is a CD22-directed antibody-drug conjugate that is currently in a phase 3 trial.[44] SGN-CD19A is an antibody-drug conjugate that is directed against CD19, a B-cell antigen. Small molecules targeting specific mutations and metabolic pathways are also in clinical development for ALL, although many are in early stages.

Disclosure

Dr Douer is on the advisory boards of Amgen, Pfizer, Sigma Tau, and Spectrum Pharmaceuticals. He has received research grants from Amgen and Sigma Tau.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.
2. National Cancer Institute. SEER Cancer Statistics Review, 1975-2011: Overview, Age Distribution of Incidence Cases by Site. 2014. http://seer.cancer.gov/csr/1975_2011/. Accessed October 29, 2014.
3. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol*. 2012;30(14):1663-1669.
4. Pulte D, Jansen L, Gondos A, et al; GEKID Cancer Survival Working Group. Survival of adults with acute lymphoblastic leukemia in Germany and the United States. *PLoS One*. 2014;9(1):e85554.
5. Douer D. Adult acute lymphoblastic leukemia: a cancer with no standard of care. *Acta Haematol*. 2013;130(3):196-198.
6. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101(12):2788-2801.
7. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000;18(3):547-561.
8. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85(8):2025-2037.
9. Rowe JM, Buck G, Burnett AK, et al; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. 2005;106(12):3760-3767.
10. Stock W, Johnson JL, Stone RM, et al. Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: results of Cancer and Leukemia Group B Study 19802. *Cancer*. 2013;119(1):90-98.
11. Chang JE, Medlin SC, Kahl BS, et al. Augmented and standard Berlin-Frankfurt-Münster chemotherapy for treatment of adult acute lymphoblastic leukemia. *Leuk Lymphoma*. 2008;49(12):2298-2307.
12. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008;111(4):1827-1833.
13. Hoelzer D, Thiel E, Löffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood*. 1988;71(1):123-131.
14. Douer D, Aldoss I, Lunning MA, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32(9):905-911.
15. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol*. 2009;27(6):911-918.
16. DeAngelo DJ, Dahlberg S, Silverman LB, et al. A multicenter phase II study using a dose intensified pediatric regimen in adults with untreated acute lymphoblastic leukemia [ASH abstract 587]. *Blood*. 2007;110(suppl 11).
17. Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. *J Clin Oncol*. 2008;26(11):1843-1849.

18. Gökbuget N, Beck J, Brandt K, et al. Significant improvement of outcome in adolescents and young adults (AYAs) aged 15-35 years with acute lymphoblastic leukemia (ALL) with a pediatric derived adult ALL protocol; results of 1529 AYAs in 2 consecutive trials of the German Multicenter Study Group for Adult ALL (GMALL) [ASH abstract 839]. *Blood*. 2013;122(21 suppl).
19. Stock S, Luger SM, Advani AS, et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): early results of U.S. Intergroup Trial C10403 [ASH abstract 796]. *Blood*. 2014. https://ash.confex.com/ash/2014/webprogram/Paper70905.html. Accessed November 19, 2014.
20. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia Version 1.2014. http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Updated June 6, 2014. Accessed November 19, 2014.
21. American Cancer Society. Leukemia-acute lymphocytic overview. 2014. http://www.cancer.org/acs/groups/cid/documents/webcontent/003054-pdf.pdf. Accessed October 29, 2014.
22. Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. *Blood*. 2013;121(7):1077-1082.
23. Oriol A, Vives S, Hernández-Rivas JM, et al; Programa Español de Tratamiento en Hematologia Group. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica*. 2010;95(4):589-596.
24. Aldoss I, Pullarkat V, Patel R, et al. An effective reinduction regimen for first relapse of adult acute lymphoblastic leukemia. *Med Oncol*. 2013;30(4):744.
25. Gökbuget N, Stanze D, Beck J, et al; German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120(10):2032-2041.
26. Fielding AK, Richards SM, Chopra R, et al; Medical Research Council of the United Kingdom Adult ALL Working Party; Eastern Cooperative Oncology Group. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109(3):944-950.
27. Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. *Cancer*. 2010;116(24):5568-5574.
28. Garcia-Manero G, Thomas DA. Salvage therapy for refractory or relapsed acute lymphocytic leukemia. *Hematol Oncol Clin North Am*. 2001;15(1):163-205.
29. Montillo M, Tedeschi A, Centurioni R, Leoni P. Treatment of relapsed adult acute lymphoblastic leukemia with fludarabine and cytosine arabinoside followed by granulocyte colony-stimulating factor (FLAG-GCSF). *Leuk Lymphoma*. 1997;25(5-6):579-583.
30. Visani G, Tosi P, Zinzani PL, et al. FLAG (fludarabine, cytarabine, G-CSF) as a second line therapy for acute lymphoblastic leukemia with myeloid antigen expression: in vitro and in vivo effects. *Eur J Haematol*. 1996;56(5):308-312.
31. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. *Ann Hematol*. 2005;84(12):792-795.
32. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol*. 2006;24(12):1917-1923.
33. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood*. 2007;109(12):5136-5142.
34. Webb MS, Harasym TO, Masin D, Bally MB, Mayer LD. Sphingomyelin-cholesterol liposomes significantly enhance the pharmacokinetic and therapeutic properties of vincristine in murine and human tumour models. *Br J Cancer*. 1995;72(4):896-904.
35. Krishna R, Webb MS, St Onge G, Mayer LD. Liposomal and nonliposomal drug pharmacokinetics after administration of liposome-encapsulated vincristine and their contribution to drug tissue distribution properties. *J Pharmacol Exp Ther*. 2001;298(3):1206-1212.
36. Webb MS, Logan P, Kanter PM, et al. Preclinical pharmacology, toxicology and efficacy of sphingomyelin/cholesterol liposomal vincristine for therapeutic treatment of cancer. *Cancer Chemother Pharmacol*. 1998;42(6):461-470.
37. O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol*. 2013;31(6):676-683.
38. Zimmerman Z, Maniar T, Nagorsen D. Unleashing the clinical power of T cells: CD19/CD3 bi-specific T cell engager (BiTE®) antibody construct blinatumomab as a potential therapy [published online September 19, 2014]. *Int Immunol*. doi:10.1093/intimm/dxu089.
39. Topp MS, Goekbuget N, Zugmaier G, et al. Anti-CD19 BiTE blinatumomab induces high complete remission rate and prolongs overall survival in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL) [ASH abstract 670]. *Blood*. 2012;120(suppl 21).
40. Topp MS, Goekbuget N, Stein AS, et al. Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) [ASCO abstract 7005]. *J Clin Oncol*. 2014;32:5(suppl).
41. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371(16):1507-1517.
42. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med*. 2013;5(177):177ra38.
43. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood*. 2012;119(12):2709-2720.
44. ClinicalTrials.gov. A study of inotuzumab ozogamicin versus investigator's choice of chemotherapy in patients with relapsed or refractory acute lymphoblastic leukemia. http://clinicaltrials.gov/ct2/show/NCT01564784. Identifier: NCT01564784. Accessed November 24, 2014.

Treating Relapsed/Refractory ALL in Older Patients: Case Presentations

Gail J. Roboz, MD
Associate Professor of Medicine
Director, Leukemia Program
New York-Presbyterian Hospital
Weill Cornell Medical Center
New York, New York

Case 1 Description

An 80-year-old woman presented to an emergency department with a myocardial infarction. During her hospital stay, laboratory work-ups revealed elevated lymphoblasts. Based on subsequent pathologic assessment, she was diagnosed with Ph-positive ALL and referred to a hematologist. The patient had multiple comorbidities, including hypertension, renal insufficiency, type 2 diabetes mellitus, and obesity. Her Eastern Cooperative Oncology Group performance status was 3 (capable of only limited self-care, and confined to a bed or chair for more than half of her waking hours).[1]

Both the patient and her family expressed a strong desire to treat the ALL. Her overall poor health status

suggested that she would be unable to tolerate extensive chemotherapy. She was therefore initially treated with the tyrosine kinase inhibitor dasatinib. During her treatment, she experienced multiple complications, including respiratory failure, pulmonary edema, acute renal failure, and hemolytic anemia. These medical issues necessitated a prolonged hospital stay, with some time spent in the intensive care unit. Despite these complications, the patient achieved a complete hematologic remission that was durable for 10 months. She was able to return home and maintain a good quality of life during this time.

The patient subsequently experienced a relapse of her ALL. By this point, her comorbidities had been effectively managed, so she began second-line treatment with vincristine sulfate liposome injection plus prednisone. She was able to receive a total of 8 cycles of the vincristine sulfate liposome injection. She showed absolute normalization of her peripheral blood cell count and no circulating blast cells, although her bone marrow continued to show evidence of disease. She became transfusion-independent, and she was able to maintain this status with a very good quality of life for approximately 3 months before her second relapse.

At the request of both the patient and her family, salvage therapy (consisting of bosutinib, hydroxyurea, and 6-mercaptopurine) was attempted. However, the patient was unable to tolerate the chemotherapy. She ultimately succumbed to refractory ALL after 2.5 months.

Case 1 Discussion

Gail J. Roboz, MD This case demonstrates that tyrosine kinase inhibitor therapy can be beneficial even in older patients with multiple comorbidities. Among older patients with ALL, between 60% and 70% are estimated to have comorbidities.[2] Furthermore, it was notable that the off-label use of vincristine sulfate liposome injection (here, in the Ph-positive setting) resulted in an additional 3 months of survival for this patient. During this time, she was able to maintain a very good quality of life, was transfusion-independent, and experienced no specific toxicities (such as neuropathy or constipation), despite her significant comorbidities.

Elias J. Jabbour, MD In 2011, investigators from the Gruppo Italiano per le Malattie Ematologiche dell'Adulto working group published the results of a study that evaluated dasatinib plus prednisone as frontline treatment for patients with ALL.[3] The median patient age in this study was 54 years (range, 24-76 years). In this study, a complete hematologic remission rate of 92% was reported, and the 20-month overall survival rate was 69% (Figure 2). The authors further noted that the benefit associated with dasatinib plus prednisone seemed to occur irrespective of age.

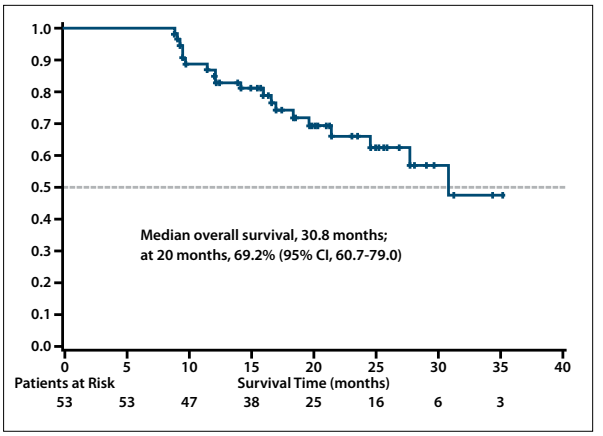


Figure 2. Overall survival in a study of dasatinib as first-line treatment for adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. Adapted from Foà R et al. *Blood*. 2011;118(25):6521-6528.[3]

In a large, prospective clinical study, an induction regimen from the European Working Group on Adult Acute Lymphoblastic Leukemia was evaluated in older patients with Ph-positive ALL.[4] This regimen consisted of vincristine, dexamethasone, and dasatinib. The rate of complete hematologic response was 94%, and the 3-year overall survival rate was 45%. Therefore, the outcomes of this trial suggest that a low-intensity chemotherapy regimen together with a tyrosine kinase inhibitor is able to achieve solid and durable responses in older patients with ALL. Because this regimen avoids exposure to the significant toxicities associated with more aggressive chemotherapies, it might be especially beneficial for older patients.

Stefan Faderl, MD This case is illustrative of the potent activity of tyrosine kinase inhibitors—even when used as a single agent—to treat Ph-positive ALL. It raises the interesting question of whether a chemotherapy backbone is even needed for the initial treatment of Ph-positive ALL. It was somewhat intuitive that in this patient—an elderly woman in poor health and with multiple comorbidities—the benefit-to-toxicity ratio would likely be better with tyrosine kinase inhibitor treatment as opposed to cytotoxic chemotherapy. But it is possible that even younger patients in otherwise good health may not require frontline treatment with both a tyrosine kinase inhibitor and an aggressive chemotherapy backbone. Given the potency of the current tyrosine kinase inhibitors, younger patients may instead be able to skip the chemotherapy or receive a less aggressive regimen.

Gail J. Roboz, MD The potency of tyrosine kinase inhibitors can be observed reproducibly in patients with ALL. This activity, combined with their relatively well-tolerated toxicity profiles, makes them a good alternative for older patients with Ph-positive ALL. Unfortunately, older patients with

ALL are far less likely to be treated with potentially curative or life-extending treatment approaches, often because of assumptions made by the physician regarding their disease-specific prognosis, general life expectancy, and comorbidities. But as shown in this patient, the use of a tyrosine kinase inhibitor resulted in a durable remission lasting 10 months, during which time the patient was able to maintain a good quality of life and interact with her family.

Stefan Faderl, MD It is also notable that the patient derived benefit from treatment with vincristine sulfate liposome injection. In 2012, this agent received accelerated approval from the FDA for the treatment of patients with Ph-negative ALL who are in second or greater relapse or whose disease had progressed following 2 or more antileukemia therapies.[5] In this patient, it had activity in the off-label setting of Ph-positive relapsed disease. The use of vincristine sulfate liposome injection for the treatment of Ph-positive relapsed ALL is currently under investigation in clinical trials.[6]

Gail J. Roboz, MD We included prednisone with the vincristine sulfate liposome injection, but at a low dose given her preexisting diabetes. I found it very interesting that the patient showed normalized blood cell counts and transfusion-independence with the vincristine sulfate liposome injection, despite having continued evidence of disease in her bone marrow.

Stefan Faderl, MD Did you have any hesitations initiating tyrosine kinase inhibitor therapy in this patient, given her significant cardiovascular-related comorbidities?

Gail J. Roboz, MD Yes, that was a significant issue that we carefully weighed throughout her treatment. While receiving dasatinib, the patient developed worsening pulmonary hypertension, which may have been related to that agent. We considered and then rejected the idea of switching her to ponatinib after her second relapse. Ponatinib is associated with risk of cardiovascular toxicity, and it has a boxed warning for vascular occlusion and heart failure; given her overall frail condition and significant preexisting cardiovascular conditions—including a prior myocardial infarction—we decided that she was not a good candidate for ponatinib.

Case 2 Description

A 62-year-old woman was diagnosed with Ph-negative and CD20-negative ALL in June 2013. She had an excellent performance status and no central nervous system disease at the time of diagnosis. She initially underwent treatment with 4 cycles of hyper-CVAD. By day 19 of her first treatment cycle, there was approximately 2% minimal residual disease in her bone marrow. However, she did subsequently achieve a complete morphologic remission with normalization of her cell counts. Unfortunately, this remission was short-lived, and a bone marrow biopsy performed approximately 1 month after her final treatment cycle showed evidence of early relapse.

The patient was subsequently enrolled in a clinical trial for inotuzumab, an antibody-drug conjugate directed against CD22. She first received treatment with inotuzumab in March 2014. She achieved what appeared to be a morphologic complete remission but with evidence of minimal residual disease. She continued with another 2 cycles of inotuzumab, which further reduced her minimal residual disease but never completely cleared it.

CAR T-cell immunotherapy was then considered for this patient as a possible salvage therapy.[7] However, a different option was needed because she had detectable minimal residual disease, and a substantial delay would be needed before the start of CAR therapy to allow for expansion of the T-cell population. A decision was made to initiate treatment with a clofarabine bridge protocol, in which clofarabine was followed by a haplo-cord transplant (involving a combination of donated cord blood stem cells plus some matched cells given from a related donor). Prior to transplant, the patient had a very hypercellular bone marrow, but she still had 0.69% detectable residual disease.

The patient is currently recovering from transplant. Thus far, she has been doing extremely well, with normalization of her blood cell counts and no residual ALL disease. However, she is struggling to recover from what appears to be posttransplant Guillain-Barré syndrome.

Case 2 Discussion

Gail J. Roboz, MD This case demonstrates that older patients who are otherwise healthy and who have a good performance status are able to tolerate a wide range of therapies. In the patient described in this case, a number of therapies were considered and tried, including hyper-CVAD, inotuzumab, CAR T-cell immunotherapy, clofarabine, and haplo-cord transplant.

Elias J. Jabbour, MD This patient would have undergone a very similar management strategy at our institution. In addition, the novel agent blinatumomab may also have been considered. Blinatumomab is part of a class of monoclonal antibodies called BiTEs. It acts by targeting the B-cell–specific antigen CD19 and also activating T cells to exert cytotoxic activity against the target B cell.[8]

Gail J. Roboz, MD That is an excellent point. We would also have tried blinatumomab, perhaps before attempting clofarabine and the haplo-cord transplant. However, at that time, blinatumomab was available only in a randomized clinical trial; we did not enroll the patient because

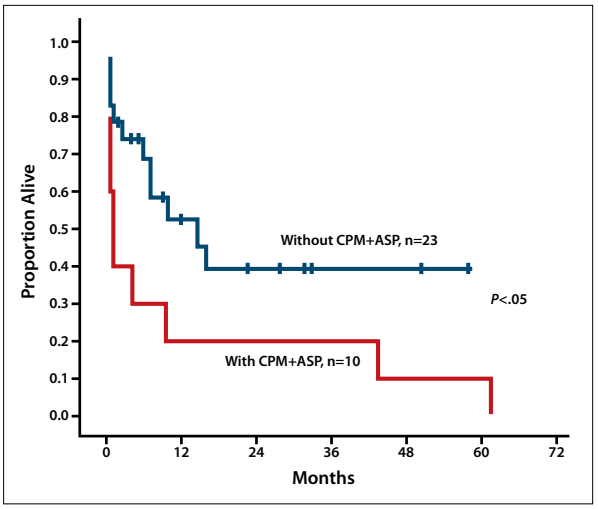


Figure 3. Overall survival among patients in the PETHEMA trial. ASP, asparaginase; CPM, cyclophosphamide; PETHEMA, Programa Español de Tratamiento en Hematología. Adapted from Sancho JM et al. *Eur J Haematol*. 2007;78(2):102-110.[9]

if she had been randomized to a chemotherapy arm, she would have been too frail to tolerate the treatment.

Stefan Faderl, MD I am intrigued by the use of clofarabine followed by the haplo-cord transplant in this patient. As you know, clofarabine does not have the highest activity in adult ALL. However, I think here it was an interesting approach for this patient.

Elias J. Jabbour, MD Was the hyper-CVAD dose-adjusted for her age? For example, did you reduce the dosage of either cytarabine or methotrexate?

Gail J. Roboz, MD We did not because she was on the lower end of what is considered older age in ALL (60 years). That, coupled with her excellent performance status, allowed us to administer the drugs at their full doses.

Stefan Faderl, MD We would have likely chosen the same initial treatment with hyper-CVAD for this patient at our institution. Do you think asparaginase could have augmented the benefit she achieved with hyper-CVAD? It is not an easy decision, because asparaginase can be difficult to tolerate for older patients.

Gail J. Roboz, MD We augmented the hyper-CVAD regimen with asparaginase during the second cycle. The patient became quite sick with abnormalities in her liver function tests and required a treatment delay, so we did not use asparaginase again.

Elias J. Jabbour, MD For ALL patients ages 40 and older, data show that adding asparaginase to the chemotherapy regimen is not beneficial. For example, the Programa Español de Tratamiento en Hematología study group showed that removing asparaginase (and cyclophosphamide) from an intensive chemotherapy induction regimen reduced the early death rate from 70% to 22% (Figure 3).[9]

Stefan Faderl, MD Incorporating asparaginase into the induction regimen is certainly more toxic, and its use in patients older than 60 years should remain limited.[2] However, I agree with the approach you took with this patient. Given the fact that you had an issue with persistent minimal residual disease, it was reasonable to try asparaginase to see if the patient could tolerate it and derive a benefit from it.

Gail J. Roboz, MD All of these are excellent points. It is important to carefully consider using asparaginase in older patients with ALL, where it has not demonstrated a specific benefit and carries with it the risk of significant toxicity. However, as was shown in this case, development of early minimal residual disease is associated with a poor prognosis, and it is important to try to achieve a completely negative minimal residual disease status prior to transplant. Because this patient had such a good performance status and was in good health overall, we thought it was worth the risk to use asparaginase to try to achieve minimal residual disease negativity as opposed to missing the opportunity altogether.

Disclosure

Dr Roboz is a consultant for Celgene, GlaxoSmithKline, AstraZeneca, Sunesis, Teva Oncology, Astex, Agios, and Novartis.

References

1. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.
2. Gökbuget N. How I treat older patients with ALL. *Blood*. 2013;122(8):1366-1375.
3. Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2011;118(25):6521-6528.
4. Rousselot P, Coudé MM, Huguet F, et al. Dasatinib (Sprycel®) and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia positive ALL aged 55 and over: final results of the EWALL-Ph-01 Study [ASH abstract 666]. *Blood*. 2012;120(suppl 21).
5. National Cancer Institute. FDA approval for vincristine sulfate liposome. 2013. http://www.cancer.gov/cancertopics/druginfo/fda-vincristine-sulfate-liposome. Accessed October 20, 2014.
6. Raj TA, Smith AM, Moore AS. Vincristine sulfate liposomal injection for acute lymphoblastic leukemia. *Int J Nanomedicine*. 2013;8:4361-4369.
7. Kochenderfer JN, Rosenberg SA. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat Rev Clin Oncol*. 2013;10(5):267-276.
8. Mølhøj M, Crommer S, Brischwein K, et al. CD19-/CD3-bispecific antibody of the BiTE class is far superior to tandem diabody with respect to redirected tumor cell lysis. *Mol Immunol*. 2007;44(8):1935-1943.
9. Sancho JM, Ribera JM, Xicoy B, et al; PETHEMA Group. Results of the PETHEMA ALL-96 trial in elderly patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol*. 2007;78(2):102-110.

Treating Relapsed/Refractory ALL in Younger Patients: Case Presentations

Elias J. Jabbour, MD
Associate Professor, Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Case 1 Description

A 24-year-old man presented with symptoms typical of ALL, including fever and fatigue lasting several days. A complete blood cell count revealed pancytopenia. His bone marrow showed the presence of 90% blasts, and staining results were myeloperoxidase-negative, CD10-positive, and CD20-positive (20% expression). His karyotype was diploid.

The patient began hyper-CVAD treatment. Data have shown that CD20 expression exceeding 20% is an adverse prognostic factor, and younger patients with this characteristic achieve improved duration of complete hematologic response and overall survival when rituximab is added to hyper-CVAD (Figure 4).[1] Therefore, given this patient's 20% expression of CD20, he was also treated with rituximab. The patient was able to receive a full 8 cycles of treatment. He responded well to this immunochemotherapy regimen with no significant toxicity, and he achieved negative minimal residual disease. He continued with maintenance therapy consisting of monthly vincristine plus prednisone pulses, weekly methotrexate, and daily mercaptopurine for 2 and a half years. His first remission lasted more than 5 years.

At the time of his first relapse, a repeat laboratory work-up showed the same characteristics as his original disease. This time, he was treated with hyper-CMAD, a modified version of hyper-CVAD in which the vincristine is replaced with vincristine sulfate liposome injection. In addition, the patient received ofatumumab, a humanized anti-CD20 monoclonal antibody approved for chronic lymphocytic leukemia. He also received intrathecal chemotherapy with methotrexate and cytarabine for a total of 8 injections. The patient responded well and went into complete hematologic remission after induction therapy. He was negative for minimal residual disease after induction and during consolidation. He experienced grade 2 peripheral neuropathy from the vincristine sulfate liposome injection, but it was effectively managed with gabapentin.

The patient had an unrelated human leukocyte antigen (HLA)-matched donor, and he was able to proceed to allogeneic stem cell transplantation. He received conditioning therapy with clofarabine plus busulfan. Following transplant, he developed graft-vs-host disease of the skin and minimal gout; both reactions resolved immediately. He entered complete hematologic remission that lasted for 22 months.

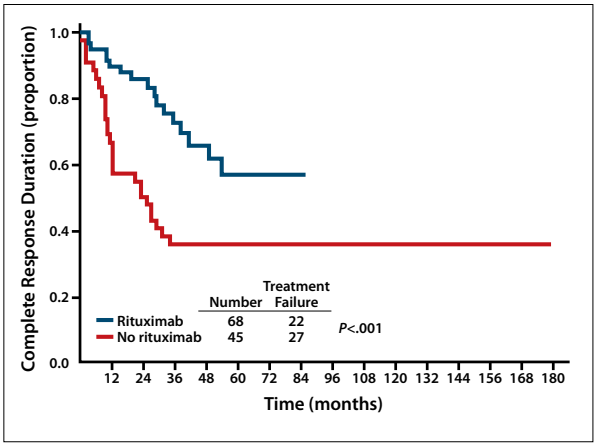


Figure 4. Duration of complete response in younger patients (<60 years) who did or did not receive rituximab in addition to hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine). Adapted from Thomas DA et al. *J Clin Oncol.* 2010;28(24):3880-3889.[1]

He then presented with pancytopenia, and a work-up confirmed relapsed disease that was CD22-positive (80% expression). He was enrolled in a clinical trial and received the CD22-directed antibody-drug conjugate inotuzumab ozogamicin as single-agent salvage therapy. After the first course, the patient achieved complete hematologic remission and was negative for minimal residual disease by flow cytometry. To date, he has received 3 cycles of inotuzumab ozogamicin. We are now proceeding to a second transplant from a different donor. Because of the risk of veno-occlusive disease with inotuzumab ozogamicin, clofarabine will not be included in the conditioning regimen. He has received ursodiol throughout the treatment as a preventive measure against veno-occlusive disorders.

Case 1 Discussion

Elias J. Jabbour, MD In this patient, the addition of rituximab to hyper-CVAD induction chemotherapy resulted in a

good outcome, with a prolonged first remission. The patient was able to respond well to subsequent therapies, but ultimately he relapsed multiple times. The median survival with inotuzumab ozogamicin is only 9 months, but if the patient can proceed to transplant, the outcome is better.[2]

Stefan Faderl, MD What was your reasoning for choosing hyper-CVAD as this patient's initial induction therapy, as opposed to an augmented BFM or pediatric-inspired protocol?

Elias J. Jabbour, MD This patient was clearly a candidate for augmented BFM therapy, which we consider for patients up to age 40 years. The decision essentially came down to the patient's preference, as he desired to have the ability to go back and forth from his home to the hospital for treatment once a month. Prospective trials of both BFM and hyper-CVAD demonstrate that there is no difference in the 3-year overall survival rate between the 2 regimens, suggesting that they are essentially equivalent for a patient such as this one.[3]

Stefan Faderl, MD What is your opinion on the difference between adding rituximab vs ofatumumab to hyper-CVAD therapy?

Elias J. Jabbour, MD We currently have a phase 2 trial evaluating the hyper-CVAD regimen in combination with ofatumumab as frontline therapy in patients with ALL.[4] The follow-up on this study is still limited, at only 12 months. In short, initial results with ofatumumab suggest that it may be slightly better than rituximab, but there is probably not a significant difference between these 2 anti-CD20 antibodies. It is important, however, to remember that the doses of these 2 antibodies may not be equivalent.

Stefan Faderl, MD What is the threshold for positive CD20 status in the ofatumumab trial?

Elias J. Jabbour, MD It is just 1%. In comparison, the threshold for rituximab is 20% expression.

Case 2 Description

A 40-year-old man presented with fever, shortness of breath, and abdominal pain. His spleen was enlarged, and he had elevated lymphocytes that were CD20-negative. He was initially treated with hyper-CVAD. Augmented BFM was not tried because the patient's age placed him above the cutoff for consideration. The patient had an initial complete hematologic response. After 2 cycles, he was found to be 0.01% positive for minimal residual disease by flow cytometry. An unrelated HLA-matched donor was identified for this patient, and he proceeded to transplant.

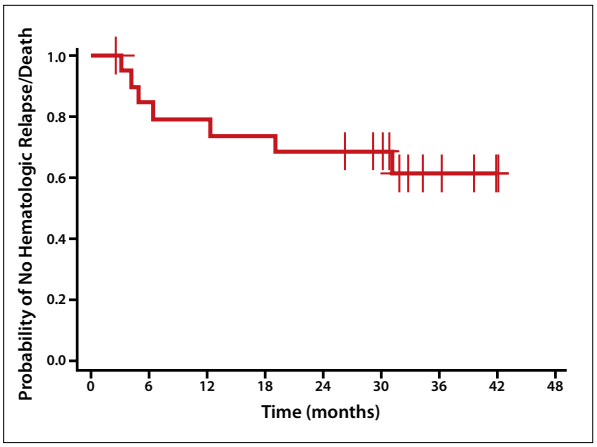


Figure 5. A follow-up analysis of a phase 2 trial evaluating blinatumomab in ALL patients with minimal residual disease showed a hematologic relapse-free survival rate of 61%. ALL, acute lymphoblastic leukemia. Adapted from Topp MS et al. *Blood.* 2012;120(26):5185-5187.[6]

He unfortunately relapsed just 4 months following transplant. Although his work-up at day 90 showed no disease, he relapsed by day 120. At relapse, he was profusely sick with B symptoms, and he again developed an enlarged spleen. He was unable to tolerate aggressive chemotherapy. We therefore initiated him on a regimen of vincristine sulfate liposome injection plus prednisone. However, he had no response to either the first or second cycle of treatment. We next switched him to an asparaginase-based regimen. However, after just the first course, he had severe elevations in his liver enzymes, and his bilirubin level reached 25 mg/dL. We were then forced to wait another 2 months for him to recover from treatment. During this time, he lost a great deal of strength with no further response.

He received a combination of clofarabine plus dexamethasone as third salvage therapy. Unfortunately, he did not respond to treatment, progressed, and ultimately died.

Case 2 Discussion

Elias J. Jabbour, MD This case highlights the importance of minimal residual disease. When negative minimal residual disease is not achieved, the patient's prognosis is severely worsened. Although transplant is the best approach, many patients will not do well.

Blinatumomab, a bispecific single-chain antibody targeting the CD19 antigen, has been shown to be a potential alternative agent for patients with chemotherapy-refractory ALL who have minimal residual disease.[5] A recently published long-term follow-up analysis of a phase 2 trial evaluating blinatumomab in this setting showed a hematologic relapse-free survival rate of 61% (Figure 5).[6] We are eager to further evaluate this agent in patients with minimal residual disease in a phase 3 clinical trial.

Stefan Faderl, MD This young patient progressed very quickly, and he never showed a robust response to treatment. It makes you wonder what in the biology of his disease made him more likely to develop resistance to therapy. For example, he may have had *BCR-ABL*–like ALL, which is associated with a poor prognosis.[7] This case highlights the need to eventually move beyond cytogenetics and *BCR-ABL* testing at the time of diagnosis. It is possible that some molecular feature might have offered the opportunity for a different treatment approach for this patient.

Elias J. Jabbour, MD Unfortunately, we are still working to develop and validate these molecular assays for ALL patients. Clinical studies are beginning to evaluate new regimens—including chemotherapy plus either dasatinib or a JAK2 inhibitor—in patients with different molecular abnormalities.

Disclosure

Dr Jabbour is a consultant for Amgen, and he has received research grants from GlaxoSmithKline.

References

1. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*. 2010;28(24):3880-3889.
2. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012;13(4):403-411.
3. Rytting ME, Thomas DA, O'Brien SM, et al. Augmented Berlin-Frankfurt-Münster therapy in adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) [published online July 17, 2014]. *Cancer*. doi:10.1002/cncr.28930.
4. ClinicalTrials.gov. Hyper CVAD plus ofatumumab in CD-20 positive acute lymphoblastic leukemia (ALL). https://clinicaltrials.gov/ct2/show/NCT01363128?term=NCT01363128. Identifier: NCT01363128. Accessed November 5, 2014.
5. Topp MS, Kufer P, Gökbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol*. 2011;29(18):2493-2498.
6. Topp MS, Gökbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood*. 2012;120(26):5185-5187.
7. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2012;2012:389-396.

A Young ALL Patient With a Long History of Treatment: Case Presentation

Stefan Faderl, MD
Chief, Leukemia Division
John Theurer Cancer Center
at Hackensack University Medical Center
Hackensack, New Jersey

Case Description

A 22-year-old woman diagnosed with Ph-negative ALL and diploid cytogenetics presented in 2008. The patient had no insurance, which upfront predicted difficulties in using certain treatments, such as bone marrow transplant or CAR T-cell immunotherapy.[1] She was initially treated with front-line hyper-CVAD induction therapy, which led to a complete hematologic remission. She continued hyper-CVAD for 5 cycles, which included 6 intrathecal treatments. She then discontinued therapy and was lost to follow-up.

Approximately 1 year later, the patient presented with relapsed disease. She was subsequently treated with the Cancer and Leukemia Group B protocol, which consists of cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase (Figure 6).[2] However, she stopped treatment mid-cycle when she became pregnant. She was able to maintain remission for nearly 1 year before her second relapse.

At this point, she was treated with a combination of vincristine and dexamethasone. Surprisingly, this treatment allowed her to regain remission, although it lasted for only 5 months. At this point, she began complaining of pain in her right knee. A magnetic resonance imaging scan revealed an extensive mass in her soft tissue. A biopsy was consistent with a diagnosis of extramedullary ALL. No other disease sites were noted, and her blood cell counts were normal.

She began treatment with the FLAG regimen. A repeat computed tomography scan following treatment showed nearly complete resolution of her extramedullary disease. She received a second cycle of FLAG, after which she experienced rapid disease progression and significant right knee pain. The pain became more diffuse, and imaging studies revealed masses around her kidneys and lymph nodes in addition to the knee.

She was then treated with augmented hyper-CVAD, which included asparaginase and an intensified schedule

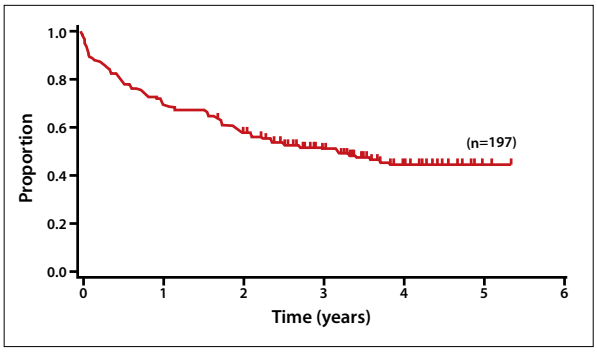


Figure 6. Overall survival, after a median follow-up of 3.5 years, in the Cancer and Leukemia Group B study 8811. Adapted from Larson RA et al. *Blood*. 1995;85(8):2025-2037.[2]

of vincristine and dexamethasone. She responded after 2 cycles, with complete hematologic remission and near complete resolution of her knee mass. She received a total of 6 augmented hyper-CVAD cycles, and she progressively became less symptomatic with each cycle.

Following treatment, she began a maintenance regimen consisting of vincristine sulfate liposome injection combined with prednisone and methotrexate. She is currently doing well on this maintenance regimen, which she has been receiving for 7 months.

Case Discussion

Stefan Faderl, MD This case describes a patient with ALL who has a long history of treatment. It illustrates the important concept that there is a possibility of managing ALL over a long period of time. Unfortunately, this patient was not insured, and we were unable to get her to a bone marrow transplant. There were obviously also issues with compliance at the start of her disease history.

Elias J. Jabbour, MD Was rituximab an option for this patient?

Stefan Faderl, MD No, she was CD20-negative, so we did not consider rituximab therapy.

Elias J. Jabbour, MD Did she acquire any Ph positivity over the course of her disease?

Stefan Faderl, MD No, she presented with Ph-negative disease and maintained it in all subsequent testing.

Gail J. Roboz, MD For ALL in general, it seems that most physicians want to move all of our newer, more potent, and less toxic therapies into the frontline setting. This approach is especially important when you consider that the number of patients who have been successfully salvaged with CAR T-cell immunotherapy and bone marrow transplants is relatively small. The consensus is that if these very potent treatments can be moved to frontline therapy, it will be less likely that the ALL will relapse and require salvage therapy.

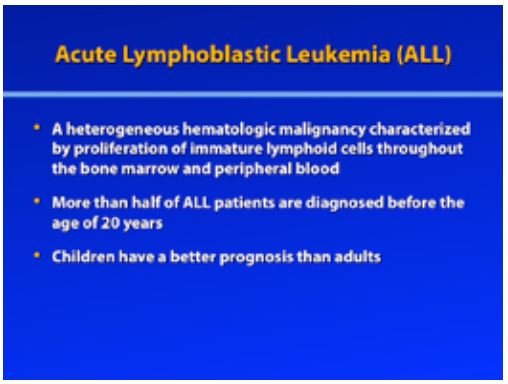
Disclosure

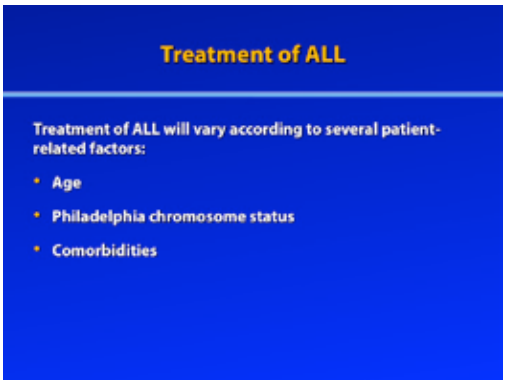
Dr Faderl has no real or apparent conflicts of interest to report.

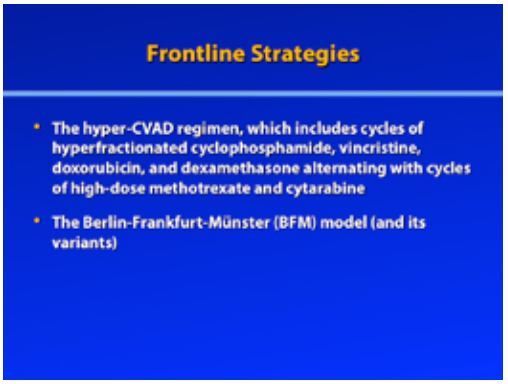
References

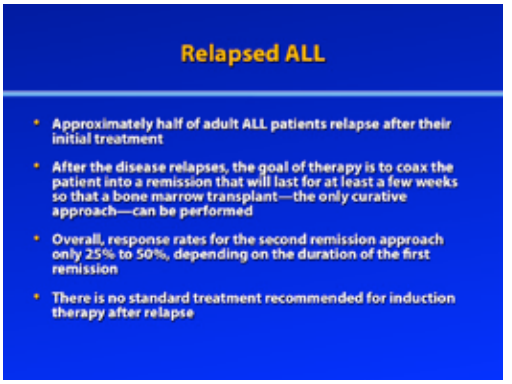
1. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6(224):224ra25.
2. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85(8):2025-2037.

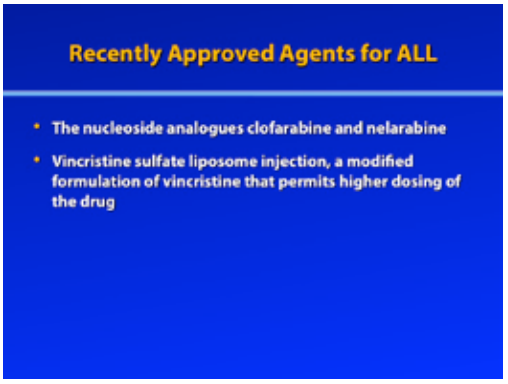
Slide Library

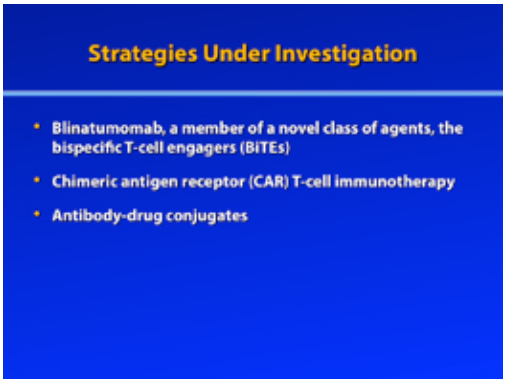












For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net