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Novel Approaches for the Interim Management of Relapsed/Refractory Acute Lymphocytic Leukemia: A Case-Study Compendium

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Abstract: The heterogeneous hematologic malignancy acute lymphocytic leukemia (ALL) represents one of the more complicated cancers in adults. Despite the large number of agents available to treat this disease, there remains no standard of care for either the frontline or relapsed/refractory settings. Although the rate of response to initial induction therapy is high, at least half of patients experience relapsed or refractory disease. Selection of salvage therapy may rely on investigational strategies in clinical trials. The goal of frontline or salvage therapy is to reduce the tumor burden so that patients can proceed to allogeneic stem cell transplant, the only treatment considered potentially curative for ALL. However, the different combination chemotherapy regimens are associated with unpredictable responses and can result in myelosuppression and other toxicities. The need for improved treatment alternatives, especially in the salvage setting, has been recently addressed with the introduction of several new therapies. Chimeric antigen receptor (CAR) T-cell therapy is a form of immunotherapy. T cells harvested from the patient are genetically engineered to express a receptor that targets a tumor-specific antigen on the tumor cell surface. Patients awaiting CAR T-cell therapy, like those awaiting stem cell transplant, often require a "bridge" treatment during the interim. A liposomal formulation of vincristine has been associated with durable responses in relapsed disease, but with less myelosuppression and neurotoxicity than standard vincristine. Other novel agents include blinatumomab and inotuzumab ozogamicin.

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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) CR/CRi 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

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

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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 nonliposomal 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*].

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Novel Approaches for the Interim Management of Relapsed/Refractory Acute Lymphocytic Leukemia: Introduction

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The heterogeneous hematopoietic malignancy acute lymphocytic leukemia (ALL) is characterized by the overproliferation of immature lymphoid cells throughout the bone marrow, peripheral blood, and other organs.[1] Most new diagnoses (60%) occur in patients younger than 20 years.[2] Approximately 24% of new cases are diagnosed in patients ages 45 years or older, and 11% are diagnosed after age 65 years.[3]

Cure rates and overall survival outcomes have significantly improved among pediatric ALL patients, but not adult patients.[4] The 5-year overall survival rate is 24.1% for patients ages 40 to 59 years and 17.7% for those ages 60 to 69 years.[4] Novel therapeutic approaches are needed for the adult ALL patient population.

As stated in guidelines from the National Comprehensive Cancer Network, "the treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy," a reflection of the number and classes of agents available to treat this disease.[3] Current standard chemotherapy regimens in the frontline setting can achieve high rates of complete remission (CR). However, half of ALL patients will develop relapsed or refractory disease, which lacks a standard treatment regimen. Additionally, adult patients with ALL who experience a disease relapse after initial therapy typically have poor long-term outcomes. Some patients may experience more favorable outcomes. Factors found to be predictive of better outcomes include younger age and a first CR (following induction therapy) lasting for at least 2 years (Figure 1).[5,6]

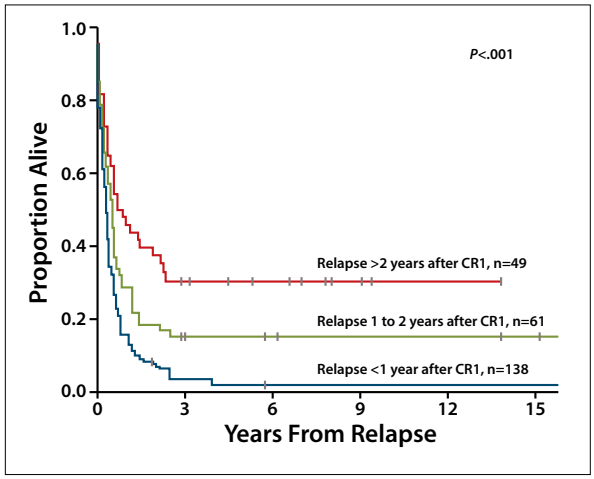

Figure 1. Overall survival according to time of relapse in trials from the PETHEMA study group. CR1, first complete remission. PETHEMA, Programa Español de Tratamiento en Hematología. Adapted from Oriol A et al. *Haematologica*. 2010;95(4):589-596.[6]

Several multiagent cytotoxic salvage therapies are commonly offered to patients with relapsed/refractory ALL. However, the toxicity profiles of these agents limit their use. The chemotherapeutic agent vincristine was reengineered into a liposomal formulation to improve toxicity and efficacy. Vincristine sulfate liposome injection was approved by the US Food and Drug Administration in 2012 for the treatment of adult patients with Philadelphia (Ph) chromosome–negative ALL in second or

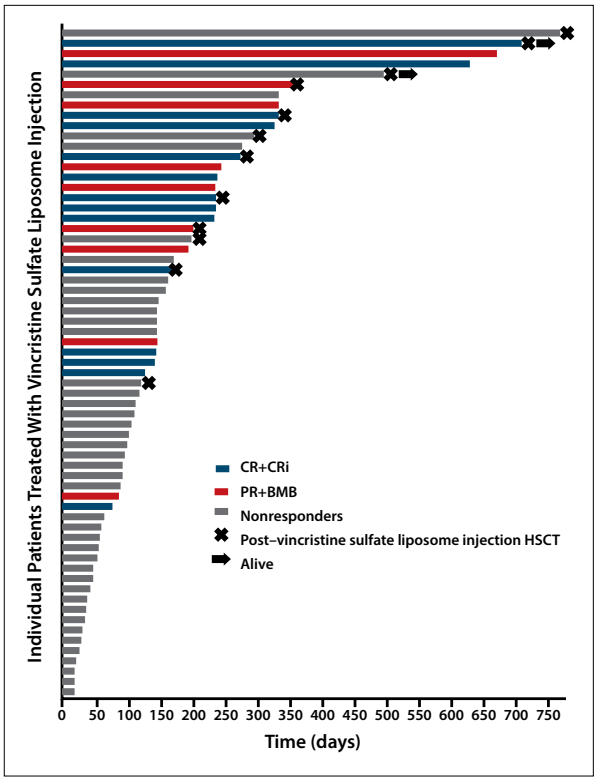

Figure 2. Outcome in a phase 2 trial of vincristine sulfate liposome injection. BMB, bone marrow blast response; CR, complete response; CRi, complete response with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; PR, partial remission; VSLI, vincristine sulfate liposome injection. Adapted from O'Brien S et al. *J Clin Oncol*. 2013;31(6):676-683.[8]

Table 1. Clinical Outcomes of a Phase 1 Trial of CAR T-Cell Therapy in Patients With Relapsed/Refractory B-Cell ALL

Characteristics	Patients (n)	%
Overall complete response to salvage chemotherapy[a]	7	44
Overall complete response to 19-28z CAR T cells	14[b]	88
Morphologic residual leukemia	7	78
Complete remission	10	63
Complete remission with incomplete count recovery	4	25
Molecular complete remission[c]	12[b]	75
Median time to complete remission, with or without count recovery (days)	24.5	–
Post-CAR T-cell allogeneic SCT[d]	7	70

[a]Overall complete response was determined without regard to molecular complete remission and included patients who did not achieve a complete count recovery.

[b]Includes 2 patients who were in molecular complete remission before CAR T-cell infusion.

[c]Molecular complete remission or minimal residual disease as determined by flow cytometry and/or deep sequencing for the index immunoglobulin heavy chain clonotype and/or quantitative polymerase chain reaction for the BCR-ABL transcript.

[d]Three patients had medical contraindications to allogeneic SCT, 2 patients in complete response declined to undergo allogeneic SCT, and 1 patient was under evaluation for an allogeneic SCT.

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; SCT, stem cell transplant.

Adapted from Davila ML et al. *Sci Transl Med*. 2014;6(224):224ra25.[11]

greater relapse or whose disease has progressed following 2 or more antileukemia therapies.[7] Approval was based on a phase 2 trial of 65 adult patients in second or greater relapse.[8] The overall response rate was 35%, including a 20% CR or CR with incomplete hematologic recovery (CRi; Figure 2). The median duration of CR was 23 weeks, with a range of 5 to 66 weeks. Long-term survival was reported in 5 patients. Vincristine sulfate liposome injection was active in patients who were refractory to other single-agent and multiagent regimens, and it was effective as third-, fourth-, and fifth-line therapy.

Immunotherapeutic approaches are also being investigated. The bispecific antibody blinatumomab is directed against the CD19 antigen. It was approved by the US Food and Drug Administration in December 2014 for the treatment of Ph chromosome–negative relapsed or refractory B-cell precursor ALL.[9] In a multicenter, phase 2 study evaluating blinatumomab in 189 patients with Ph chromosome–negative relapsed/refractory ALL, 43% of patients achieved a CR/CRi.[10] However, the median overall survival was only 6.1 months. In addition, the antibody drug toxin inotuzumab ozogamicin, which is directed against the CD22 antigen, is in advanced phase 3 clinical trials of patients with relapsed or refractory ALL.

Chimeric antigen receptor (CAR) T-cell therapy is another form of immunotherapy. T cells harvested from the patient are genetically engineered to express a receptor that targets a tumor-specific antigen on the tumor cell surface. (In B-cell ALL, the target is most often the CD19 antigen.) These genetically modified T cells are expanded ex vivo, and then reinfused into the patient. CAR T-cell therapy has shown promising results in ALL, with CRs in nearly 90% of patients (Table 1).[11]

Preparation of CAR T cells can take up to 6 weeks. Patients awaiting CAR T-cell therapy, like those awaiting stem cell transplant, often require a "bridge" treatment during the interim. The case reports in this monograph will discuss the use of new combination and sequential therapeutic strategies in relapsed/refractory ALL. Recently published data suggest that these novel and emerging approaches, used in combination with stem cell transplant, can optimize outcomes.

Disclosure

Dr Wang has served on advisory boards for Sigma Tau and Spectrum Pharmaceuticals. She is on the speakers bureau for Incyte.

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A Man With Pre–B-Cell, CD20-Negative ALL

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Case Description

A 30-year-old African American man was diagnosed by stem cell biopsy with pre–B-cell ALL that was CD20-negative. He underwent initial treatment with a dose-intensive augmented Berlin-Frankfurt-Münster (BFM) regimen[1] consisting of 5 weeks of induction therapy with vincristine, prednisone, L-asparaginase, daunomycin, cytarabine, and methotrexate.

He responded very well by day 14. By day 28, testing for minimal residual disease was negative. Following induction treatment, he underwent consolidation with augmented BFM. This protocol consisted of a 9-week course of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, L-asparaginase, and methotrexate, as well as radiotherapy for central nervous system prophylaxis.[1]

The patient then underwent 2 years of maintenance therapy, consisting of weekly methotrexate, plus daily 6-mercaptopurine and monthly pulses of vincristine plus prednisone. He tolerated this treatment well. He did not show evidence of a B-cell phenotype, and he had a diploid karyotype. By the end of his 2 years of maintenance therapy, he had developed advanced cytopenia. A repeat bone marrow biopsy showed that his disease had relapsed. The cells were found to be the same immunophenotype as those at the original diagnosis. He remained CD20-negative.

The patient was initiated on a fractionated regimen of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), alternating with high-dose methotrexate plus cytarabine.[2] Although he was referred for transplant, no donor was available. He achieved a remission that was durable for 4.5 months. During that time, he experienced treatment-related complications including infection and myelosuppression, but they were effectively resolved. At relapse, he received 2 cycles of inotuzumab ozogamicin[3]; however, he showed absolutely no response to this therapy.

As mentioned, the patient lacked a donor for allogeneic stem cell transplant, and he did not qualify for any ongoing clinical trials. He therefore began the process of T cell collection to prepare for CAR T-cell therapy.[4] At this time,

he also received a salvage chemotherapy regimen consisting of vincristine sulfate liposome injection combined with dexamethasone and pegylated L-asparaginase.[5] Although the patient was very ill, he ultimately achieved a third remission.

The patient underwent infusion of his genetically altered CAR T cells. He developed cytokine-release syndrome, but it was not severe and he recovered. He achieved a CR that was maintained for 4 months. During this remission, he developed a fulminant fungal sinusitis mucormycosis that led to his death despite inpatient hospitalization.

Case Discussion

Elias J. Jabbour, MD This case illustrates the effectiveness of a salvage chemotherapy regimen in the setting of relapsed ALL. Importantly, a combination regimen was used as salvage therapy, because single-agent salvage regimens are associated with low response rates (20%), and long second remissions are rare.[6] In a retrospective analysis of adults with ALL who received second salvage therapy, a CR was seen in 18% of patients receiving combination therapy and 4% of patients treated with a single agent.[7]

At the time of the patient's salvage treatment, the goal was to achieve the best disease control in order for him to be able to proceed to CAR T-cell therapy.

Dan Douer, MD What was the dose of inotuzumab ozogamicin administered to this patient?

Elias J. Jabbour, MD We administered inotuzumab ozogamicin as a single agent at a dose of 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 of a 3-week cycle. This dose was used in the ongoing INO-VATE ALL (Study 1022; Efficacy and Safety of Inotuzumab Ozogamicin [INO] vs Standard of Care [SOC] in Salvage 1 or 2 Patients With Acute Lymphoblastic Leukemia [ALL]: An Ongoing Global Phase 3) clinical trial. INO-VATE ALL is an open-label, randomized, phase 3 study evaluating the safety and efficacy of inotuzumab ozogamicin compared with standard-of-care chemotherapy in 326 adult patients with relapsed or refractory CD22-positive ALL.[8] Inotuzumab ozogamicin was administered once weekly for 3 weeks during a cycle lasting 21 to 28 days, for up to 6 cycles. Chemotherapy options included fludarabine, cytarabine, and granulocyte-colony stimulating factor (FLAG); high-dose cytarabine; and cytarabine plus mitoxantrone.

The primary endpoints of this study are hematologic remission (defined as CR/CRi) and overall survival. Secondary endpoints include progression-free survival, volume of distribution and systemic clearance for inotuzumab ozogamicin in the serum, duration of response, rate of stem cell transplant, minimal residual disease, cytogenetics, safety, and quality of life. An initial report from the study showed that the primary endpoint was met. The rate of CR/CRi was 80.7% in the inotuzumab ozogamicin arm vs 33.3% in the chemotherapy arm (P<.0001).[9] No new or unexpected safety issues were identified.

Dan Douer, MD This study is the only randomized controlled trial demonstrating such a high response rate in the relapsed or refractory ALL setting. It should be noted that approximately half of the patients were classified as CR and the other half as CRi. The overall survival data are not available.

Elias J. Jabbour, MD In our experience, patients who have received more than 1 salvage regimen have a weaker response to treatment with inotuzumab ozogamicin. Still, it was surprising that our patient had absolutely no response to this therapy, especially given that he did not have the characteristics associated with a poor response to inotuzumab ozogamicin treatment—that is, he did not have a complex karyotype or a high blast percentage.[10]

A single-arm study of inotuzumab ozogamicin, reported in 2013, evaluated 2 different schedules of the agent in patients with relapsed or refractory ALL.[11] A total of 90 patients were treated in this study; of these, 68% had received at least 2 or more salvage therapies. The first 49 patients received a single dose of inotuzumab ozogamicin (1.3 to 1.8 mg/m^2 every 3 to 4 weeks), and the second set of 41 patients received a modified schedule of weekly inotuzumab ozogamicin (0.8 mg/m^2 on day 1, followed by 0.5 mg/m^2 on days 8 and 15 every 3 to 4 weeks). This latter schedule was used based on in vitro data suggesting higher efficacy with more frequent exposure. The overall response rate across all patients was 58% (of these, 19% were a CR, 30% were a CRi, and 9% were a stem cell CR with no recovery of counts). The response rates for both the single-dose per cycle and the once-weekly schedules were similar (57% vs 59%, respectively). Overall, the median survival was 6.2 months. Survival was longest among patients who had received only 1 prior salvage regimen (9.2 months), as compared with those who had received 2 (4.3 months) or 3 or more (6.6 months; Figure 3).

Eunice S. Wang, MD Interestingly, the median overall survival achieved with blinatumomab also appears to be affected by the number of prior salvage therapies.

Elias J. Jabbour, MD Yes, that is correct. The initial study of blinatumomab in relapsed and refractory ALL enrolled patients with essentially minimal disease, who had received only 1 prior salvage therapy. In that study, the median overall survival was 9.8 months.[12] A confirmatory phase 2 trial included 189 patients, a majority of whom had received 2 or more prior salvage therapies.[13] This trial reported a shorter

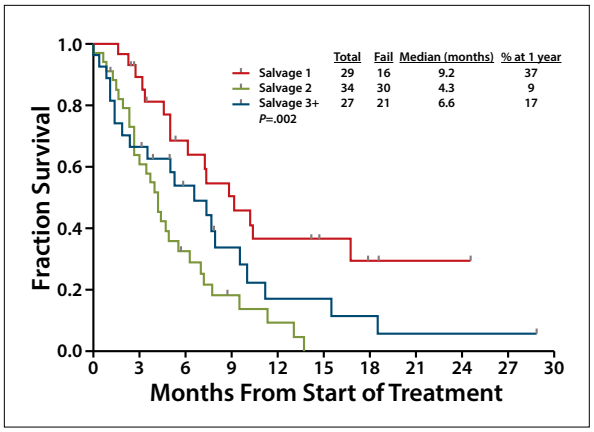

Figure 3. Survival according to number of salvage therapies in a single-arm study of inotuzumab ozogamicin. Adapted from Kantarjian H et al. *Cancer*. 2013;119(15):2728-2736.[11]

median overall survival of 6.1 months (Figure 4), closer to what was observed in the single-arm inotuzumab ozogamicin study of similar patients.[11]

Dan Douer, MD I found it interesting that you chose to coadminister pegylated L-asparaginase and dexamethasone with the vincristine sulfate liposome injection. In the phase 1 clinical trial of vincristine sulfate liposome injection, it was coadministered with dexamethasone but not with pegylated L-asparaginase.[14] Have you studied the addition of pegylated L-asparaginase to vincristine sulfate liposome injection?

Elias J. Jabbour, MD We have not directly studied the combination of pegylated L-asparaginase with vincristine sulfate liposome injection. However, we have evaluated the substitution of vincristine sulfate liposome injection for conventional vincristine in the hyper-CVAD regimen (termed *hyper-CMAD*).

In an ongoing study in patients with treatment-naive ALL, we have observed a high rate of grade 3 or 4 peripheral neuropathy (approximately 40%), which is much higher than the 15% that was previously observed with single-agent vincristine sulfate liposome injection in the pivotal phase 2 trial.[15] In this study, the vincristine sulfate liposome injection was initially scheduled to be administered in both the hyper-CMAD regimen as well as with the methotrexate plus cytarabine regimen (therefore, twice per cycle). This approach differs from the traditional hyper-CVAD regimen, in which conventional vincristine is administered only once per cycle. Additionally, vincristine sulfate liposome injection was administered at 2.25 mg/m^2 in each cycle. However, the significant neuropathy we observed prompted us to drop the dose of vincristine sulfate liposome injection to 2 mg/m^2 delivered only during the odd cycles. This approach has proven to be much more tolerable, and in fact this schedule was used for this particular patient. He did show a good response to the vincristine sulfate liposome injection–based regimen.

Dan Douer, MD We have a slightly different approach with vincristine sulfate liposome injection as a single agent. Instead of lowering the dose, we increase the dose interval from 1 week to 2 weeks. This increased interval also allowed us to reduce the incidence of neuropathy while maintaining good responses. So it seems that either lowering the dose or increasing the interval of vincristine sulfate liposome injection are potential strategies to reduce the risk of neuropathy, while still having an impact on patient outcomes.

The pivotal phase 2 study of vincristine sulfate liposome injection excluded patients who developed grade 2 or higher residual persistent neuropathy after prior vincristine exposure.[15] This criteria may have impacted the rates of neuropathy reported in that study (which were 29% for all grades, 15% for grade 3, and no grade 4). It is possible that now, with more widespread use in the clinic, the real rates of neuropathy are higher.

Overall, it is important to remember that vincristine is a neurotoxic drug, even if the increased doses of vincristine that are given in the sulfate liposome injection formulation may not be associated with the higher rate seen with the standard formulation. But to Dr Jabbour's point, it is apparent that the neuropathy associated with its use can be effectively managed with simple strategies, such as reducing the dose or increasing the dosing intervals.

Eunice S. Wang, MD Do you use the vincristine sulfate liposome injection, dexamethasone, and pegylated L-asparaginase combination in older patients with relapsed or refractory ALL, given the fact that pegylated L-asparaginase is generally not very well tolerated?

Elias J. Jabbour, MD Typically, we do not strongly advocate the use of pegylated L-asparaginase, especially in the elderly. We are more apt to use it in the setting of relapsed or refractory disease, but even then we closely monitor the patient for signs of toxicity. We are also very conservative with its administration, and do not exceed 1500 IU.

Dan Douer, MD At our center, we do not administer pegylated L-asparaginase to patients older than 60 years because toxicities—especially liver toxicity—are often too high in these patients. It is unclear if a lower dosage would still be as efficient. Dose adjustments based on serum asparaginase enzymatic activity are being considered, but an algorithm for such an approach should be well-validated. The Cancer and Leukemia Group B (CALGB) 10403 clinical trial of pegylated L-asparaginase was limited to adults ages 39 years or younger.[16] Pegylated

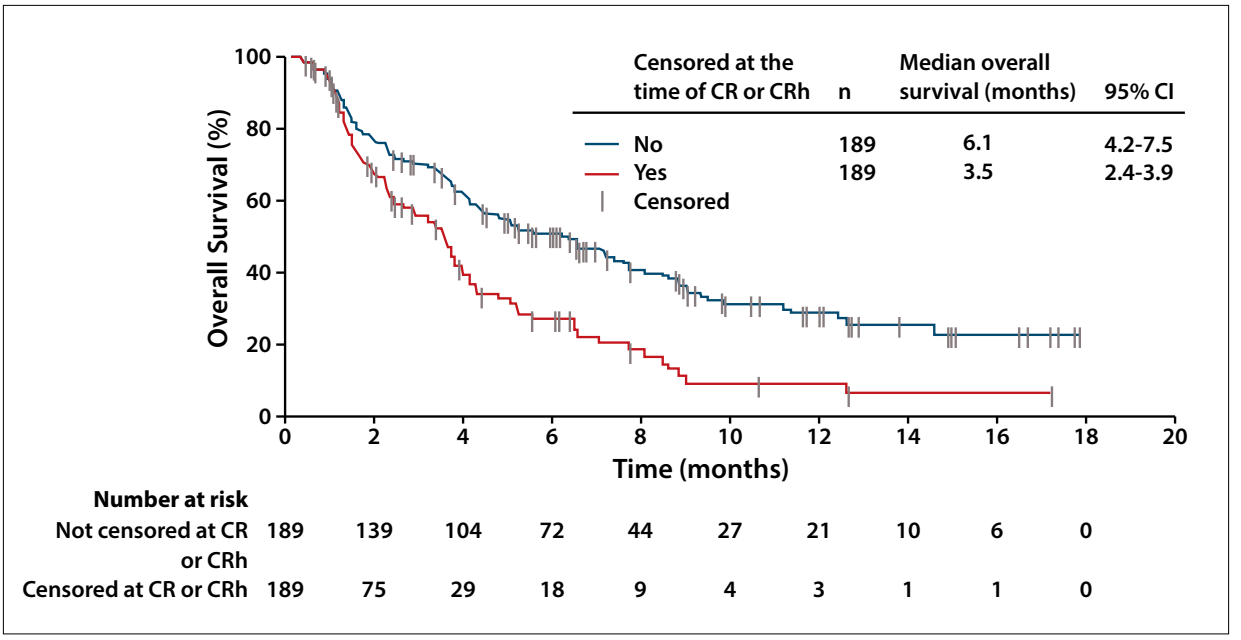

Figure 4. Overall survival in a phase 2 trial of blinatumomab. CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts. Adapted from Topp MS et al. *Lancet Oncol*. 2015;16(1):57-66.[13]

L-asparaginase, which is used in contemporary multiagent chemotherapy regimens, is associated with a high rate of liver toxicity ranging from 25% to 35% (although it is reversible).[17,18] Could the liver toxicity associated with pegylated L-asparaginase increase the toxicity of vincristine sulfate liposome injection? Vincristine is excreted primarily by the liver, and the pharmacokinetics of vincristine sulfate liposome injection are thought to be altered by hepatotoxicity arising from pegylated L-asparaginase.

Elias J. Jabbour, MD The risk of liver toxicity is augmented by the combination of the 2 drugs beyond that seen with either agent individually. Our experience with a regimen of methotrexate, vincristine, pegylated L-asparaginase, and dexamethasone (MOAD)[19] shows an increase in bilirubin levels. In fact, this toxicity often limits the ability to administer more than 1 cycle of MOAD. However, by reducing the dose and/or increasing the duration between doses, we are able to administer this regimen with minimal liver damage.

Dan Douer, MD The timing of administration of pegylated L-asparaginase in relation to other drugs within a regimen is critical. In children and adults, pegylated L-asparaginase has a very long half-life,[20,21] and synchronization of its delivery with other agents helps prevent and manage higher vincristine toxicity.

Eunice S. Wang, MD When this regimen is administered together with pegylated L-asparaginase and dexamethasone, do you continue the vincristine sulfate liposome injection on a weekly basis?

Elias J. Jabbour, MD No, we do not administer weekly vincristine sulfate liposome injection; instead it is given twice per cycle (for example, on days 4 and 11 of a 28-day cycle). At least initially, dexamethasone is followed by pegylated L-asparaginase on days 4 and 11 as well, but we closely monitor the patient.

Eunice S. Wang, MD Do you think that the use of corticosteroids in this patient predisposed him to the aggressive fulminant fungal infection that ultimately led to his death?

Elias J. Jabbour, MD The patient's long-term exposure to corticosteroids played a large role in both the development of this infection and his inability to adequately clear it. I should clarify, though, that I do not think the infection resulted directly from combining dexamethasone with the vincristine sulfate liposome injection during his final chemotherapy regimen. I attribute the fungal infection primarily to his long-term, cumulative exposure to corticosteroids over several regimens that ultimately contributed to immunosuppression. The infection was severe; within 2 days of the initial diagnosis, the fungus had invaded his central nervous system, and he was experiencing diplopia.

In retrospect, it could be considered that the dexamethasone should have been omitted from this patient's

last chemotherapy regimen. That triple-drug combination was chosen because we wanted him to achieve the best possible response to ensure an optimal outcome with the CAR T-cell therapy. When used as a single-agent in the heavily pretreated setting, vincristine sulfate liposome injection is associated with a 20% rate of hematologic CR/CRi.[15] Our goal to increase this rate prompted us to use the combination regimen.

Eunice S. Wang, MD At our center, we do not administer high-dose corticosteroids within a week of the planned admission to begin collection of the T cells. This is primarily because of the potential immunosuppression, and because we do not want the patient's T cells to be suppressed before collection.

Elias J. Jabbour, MD In this patient's case, his last use of corticosteroids before undergoing T-cell collection was aligned with your institution's policy. Specifically, his last dexamethasone administration occurred 4 weeks prior to his infusion.

Dan Douer, MD Mucormycosis infection is not a common fungal infection in patients with acute leukemias who have severe neutropenia, and it is more likely to be associated with the prolonged use of corticosteroids,[22] as in this patient.

Disclosure

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

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A Woman With CD19-Positive, B-Cell ALL

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Case Description

A 30-year-old woman was initially diagnosed with B-cell ALL. Cytogenetics and immunophenotyping revealed her disease to be Ph chromosome–negative and CD19-positive. She first received induction therapy with a fractionated hyper-CVAD regimen (consisting of cyclophosphamide, vincristine, doxorubicin, and dexamethasone), which was alternated with high-dose methotrexate plus cytarabine.[1]

She responded well, achieving a CR. She proceeded to maintenance therapy with weekly methotrexate, plus daily 6-mercaptopurine and monthly pulses of vincristine plus prednisone. After approximately 1.5 years of maintenance treatment, the patient experienced a disease relapse.

Her first salvage therapy, consisting of ifosfamide, etoposide, and dexamethasone, led to a CR. During this time, she was referred for stem cell transplant and was found to have a human leukocyte antigen (HLA)-matched sibling donor. After she recovered from the salvage chemotherapy regimen, she underwent an allogeneic stem cell transplant. Although she recovered well from transplant, she experienced a second relapse approximately 6 months after completing the transplant procedure.

Our next approach was to place this patient into the ongoing CAR T-cell study protocol.[2,3] This ongoing phase 1 trial is enrolling patients with CD19-positive relapsed or refractory ALL. Preparation of CAR T cells can take 4 to 6 weeks. During this time, we administered vincristine sulfate liposome injection. Treatment with CAR T-cell therapy led to a third CR that has been sustained now for more than 6 months.

Stem cell transplant remains the only established strategy with the potential to cure ALL.[4] It remains to be proven whether CAR T-cell therapy will also be able to achieve a cure in these patients. We have discussed with this patient the possibility of undergoing a second stem cell transplant. However, she has refused thus far. She continues to be routinely followed.

Case Discussion

Dan Douer, MD There is no standard treatment for patients with relapsed or refractory ALL. Despite the large number of available agents, and the even larger number of combinations, patient outcomes after first salvage are very discouraging.[4] In a study from the MD Anderson Cancer Center of adult patients with relapsed disease, treatment with multiple regimens led to a CR rate of only 31% and a median overall survival of 5 months.[5] More recently, the PETHEMA (Programa Español de Tratamiento en Hematología) study also demonstrated that 45% of patients were able to achieve a second CR with salvage therapy, with a median overall survival of 4.5 months.[6] Data from adult patients with ALL who relapsed following frontline therapy in the Medical Research Council United Kingdom Acute Lymphoblastic Leukaemia Trial XII/Eastern Cooperative Oncology Group (ECOG) 2993 trial showed a median survival of 5.3%.[7] Additionally, patient responses tend to worsen with each subsequent salvage therapy.

The duration of the first remission response has been shown to be a critical determinant of patient outcome, with shorter durations associated with worse overall outcomes after relapse. For example, an assessment of the 4 consecutive risk-adapted trials from the PETHEMA Study Group reported that a good outcome following salvage therapy was more likely in patients younger than 30 years and patients with a durable first remission lasting longer than 2 years.[6] Two-year overall survival was 36% when remission was more than 2 years vs 17% when remission was 2 years or less (P<.001).[6]

In this case, the patient's first relapse occurred during the maintenance phase of the treatment, after a remission lasting approximately 1.5 years. This relatively durable remission, coupled with the patient's young age, portended a better outcome with salvage therapy. The patient eventually did achieve a CR, and she was able to proceed to allogeneic stem cell transplant. Unfortunately, transplant did not prove curative, and she relapsed shortly thereafter.

We opted for CAR T-cell therapy as second salvage treatment. In a study of 16 patients with relapsed or refrac-

tory ALL, CAR T-cell therapy was associated with a CR rate of 88%, and most of the patients were able to bridge over to allogeneic stem cell transplant.[8] A study from Memorial Sloan Kettering Cancer Center of 28 patients also reported an 88% CR rate, with a 6-month survival of 57%.[9] In comparison, the available salvage chemotherapies typically achieve a remission rate of approximately 30%.[4]

An important drawback to CAR T-cell therapy is the length of time required between the collection of T cells and the point at which the genetically modified CAR T cells can be administered back to the patient, which can take up to 6 weeks.[10,11] CAR T-cell treatment involves several steps, beginning with T-cell harvesting by leukapheresis, followed by processing in the laboratory that includes genetic modification using a viral vector (typically retroviral or lentiviral in origin) that allows for the T cells to recognize CD19-expressing pre–B ALL cells. This step also induces the cells to expand following antigen recognition in vivo after infusion.[4] Known issues regarding the safe use of these viral vectors necessitate a rigorous quality control process. Eventually, the CAR T cells are infused back into the patient.[12,13] After the infusion, tumor debulking can occur rapidly, often within the first week.[4,8,10] Emerging methodologies and commercialization of this processing will hopefully decrease this turnaround time in the near future.

While the cells are being prepared in the laboratory, the disease continues to progress and worsen, and a bridging treatment is needed (which is discussed below). It is sometimes necessary to prioritize patients to determine who will have earlier access to their newly modified cells. Blinatumomab, which is approved for relapsed or refractory ALL,[14] would also have been a good alternative salvage option for this patient. However, blinatumomab is associated with a lower CR rate of 40% when used as a salvage therapy.[15,16] In principle, blinatumomab has a mechanism of action that is relatively similar to CAR T-cell therapy, in that they both target CD19-positive cells.[16,17] There is concern that blinatumomab used before CAR T cells could eliminate the cells expressing the CD19 target, thereby reducing the target for the CAR T cells. So far, this has not been a common problem.

Treatment with inotuzumab ozogamicin via a clinical trial would have been another reasonable option as salvage therapy for this patient. Because inotuzumab ozogamicin targets the B-cell–specific ligand CD22, there is a possibility that its use could deplete the B-cell pool and thereby reduce the CAR T-cell target.[17] The sequencing of blinatumomab and inotuzumab ozogamicin, together with CAR T-cell therapy, will likely be an essential consideration when treating relapsed or refractory ALL in the salvage setting.

We have used vincristine sulfate liposome injection as an alternative strategy to achieve remission before administration of CAR T-cell therapy. We have attempted to use vincristine sulfate liposome injection in combination with corticosteroids. However, we try to avoid concomitant corticosteroid use when the plan is to proceed to CAR T-cell therapy, as corticosteroids are thought to reduce the efficacy of this therapy.[18] Use of vincristine sulfate liposome injection to reduce tumor burden before CAR T-cell therapy is attractive for several reasons. Importantly, it is not myelosuppressive. The pivotal phase 2 trial reported relatively low rates of neutropenia (all grade: 17%; grade 3/4: 16%), anemia (all grade: 12%; grade 3/4: 5%), thrombocytopenia (all grade: 9%; grade 3/4: 7%), and febrile neutropenia (all grade: 8%; grade 3/4: 3%), especially when considered in comparison with cytotoxic chemotherapy.[19] Therefore, by using vincristine sulfate liposome injection, we can typically avoid this adverse event, which is especially important in light of the potential toxicities associated with CAR T-cell therapy.[18]

The main toxicity observed with vincristine sulfate liposome injection is neurotoxicity, which can be effectively managed with dose reduction and/or by increasing dosing intervals. As reported in the pivotal phase 2 trial, vincristine sulfate liposome injection was associated with a 20% CR rate.[19] An additional 15% of patients achieved either a partial response or a bone marrow blast response, equating to an overall response rate of 35%. This is important because CAR T-cell therapy can be effective in patients who start treatment with less than a CR. In contrast, the success of stem cell transplant is highly dependent upon achievement of a CR prior to the procedure.

It is important to minimize tumor burden before initiation of CAR T-cell therapy because a higher number of tumor cells corresponds to an increased release of cytokines, raising the risk of severe cytokine-release syndrome (Figure 5).[20] We use a specific protocol to define the degree of cytokine-release syndrome observed with CAR T-cell therapy.[8] Symptoms of cytokine-release syndrome include fever, hypotension, respiratory failure, and multisystem organ failure requiring treatment in an intensive care unit. We closely monitor the levels of C-reactive protein, which are thought to correlate to the severity of cytokine-release syndrome.[8,18]

Another important side effect of CAR T-cell therapy is neurotoxicity in the form of encephalopathy, clinically manifesting as changes in mental status or seizures.[18] The neurologic toxicities observed with CAR T-cell therapy are not related to the cytokine-release syndrome, and they have no relationship to the neurotoxicity associated with vincristine sulfate liposome injection. The encephalopathy can be brief and self-limiting, but occasionally it is severe and progressive, requiring corticosteroid treatment. Notably, the neurotoxicity observed with CAR T-cell therapy is more severe than that associated with blinatumomab.

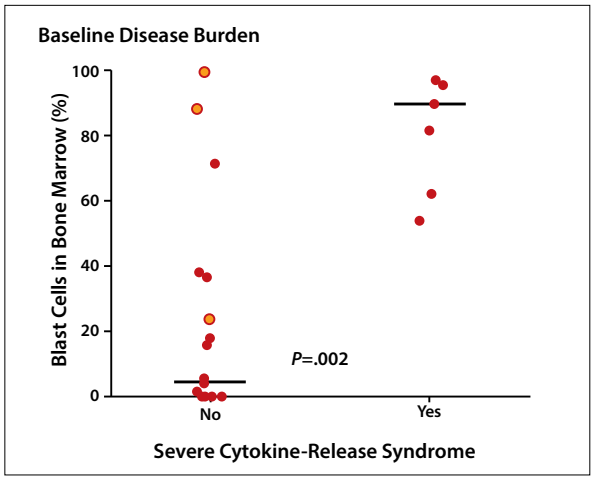

Figure 5. In a study of CAR T-cell therapy, degree of tumor burden was related to the development of severe cytokine-release syndrome. CAR, chimeric antigen receptor. The red circles indicate complete remission, the orange circles indicate no response, and the horizontal lines are the medians. Adapted from Maude SL et al. *N Engl J Med*. 2014;371(16):1507-1517.[20]

Elias J. Jabbour, MD If the clinical trial of inotuzumab ozogamicin leads to the drug's approval, it will join blinatumomab and vincristine sulfate liposome injection as options for salvage therapy of ALL. Do you anticipate that these agents will be used as monotherapy or in combination with each other?

Dan Douer, MD Thus far, blinatumomab has been used as monotherapy, at least in the setting of relapsed or refractory ALL. However, it would be very interesting to evaluate whether combining blinatumomab with chemotherapy would increase efficacy without adding toxicity, including in the frontline setting. A randomized, phase 3 clinical trial led by ECOG is recruiting adult patients (ages 35 to 70 years) with newly diagnosed, Ph-negative, pre–B-cell ALL to evaluate combination chemotherapy given with or without blinatumomab as frontline treatment.[21] In a similar fashion, other studies are being designed to evaluate inotuzumab ozogamicin in combination with chemotherapy as frontline therapy for ALL.[22]

Vincristine sulfate liposome injection is an obvious choice to begin with when evaluating novel combinations in the relapsed/refractory setting. It is already an approved agent, with a known response rate and an established toxicity profile. Likewise, we have learned a great deal about the safety and efficacy of blinatumomab. Therefore, it makes sense to investigate these agents in combination. Combining inotuzumab ozogamicin with vincristine sulfate liposome injection could also be considered. Unfortunately, even with the higher and more durable responses expected with using these agents in combination as opposed to as monotherapy, a cure is unlikely. Patients with ALL still require stem cell transplant to have the chance to achieve a cure.[4] It is possible that CAR T-cell therapy may also be curative, but this remains to be proven.

Elias J. Jabbour, MD One of my main concerns with using inotuzumab ozogamicin as part of a combination regimen is its apparent risk for veno-occlusive disease. In a single-institution study of inotuzumab ozogamicin monotherapy in patients with relapsed or refractory ALL, veno-occlusive disease was observed in 1 of 14 patients who underwent allogeneic stem cell transplant after weekly inotuzumab ozogamicin.[23] It occurred in 5 of 22 patients who underwent allogeneic stem cell therapy following a single dose of inotuzumab ozogamicin. The occurrence of veno-occlusive disease might be related to the preparative regimen used. Among the patients who experienced veno-occlusive disease, the preparative regimen included 2 alkylating agents in 5 patients, and 1 alkylating agent in 1 patient (P=.02).

The combination of inotuzumab ozogamicin and vincristine sulfate liposome injection is worthy of investigation. It is possible that the schedule and dose currently used for inotuzumab ozogamicin monotherapy administration (0.8 mg/m^2 on day 1, followed by 0.5 mg/m^2 on days 8 and 15 every 3 to 4 weeks) might be too intensive when used in combination with another agent.[23] Therefore, it perhaps should be explored at a lower dose in combination regimens.

Dan Douer, MD Is veno-occlusive disease the primary serious adverse event of concern with inotuzumab ozogamicin?

Elias J. Jabbour, MD Yes. Veno-occlusive disease is directly a result of the agent being a calicheamicin derivative. The similarly designed antibody-drug conjugate gemtuzumab ozogamicin is likewise associated with an increased risk for veno-occlusive disease.[24] I agree with the evidence from the clinical study thus far, that avoiding the use of 2 alkylating agents during the preparative regimen is an important means by which to lower the risk of veno-occlusive disease in this setting.[23]

Eunice S. Wang, MD The CALGB is moving forward with two phase 2 trials in the cooperative group setting. The first study is for younger patients with ALL who have positive minimal residual disease. Blinatumomab will be incorporated into consolidation therapy after patients achieve a CR with minimal residual disease.[25] The second study is currently recruiting elderly patients (ages 65 years or older) with ALL. It will combine blinatumomab with a corticosteroid, and administer this combination either with a tyrosine kinase inhibitor (in Ph-positive patients)

or without one (in Ph-negative patients).[26] Of note, one aim of this latter trial will be to determine how well these elderly patients tolerate blinatumomab, in contrast to the standard combination chemotherapy regimens, with their known toxicities, that this population typically receives.

Elias J. Jabbour, MD At our center, we are currently involved in a clinical trial of frontline treatment for elderly patients with ALL. The trial is combining inotuzumab ozogamicin with a mini–hyper-CVD regimen, which consists of cyclophosphamide and dexamethasone at 50% dose reduction, methotrexate at 75% dose reduction, and low-dose cytarabine (without anthracycline).[27] Rituximab and intrathecal chemotherapy are given in the first 4 courses. Inotuzumab ozogamicin was administered on day 3 of each of the first 4 courses. The results have been very encouraging thus far, especially for elderly patients: a 96% overall response rate, including a CR rate of 81%. Additionally, it seems that this combination is prolonging survival compared with the hyper-CVD regimen alone, with a 1-year overall survival of 78%.

We are also initiating a clinical trial in younger adults (ages 40 to 60 years) with ALL. The planned regimen for this study is 4 cycles of hyper-CVAD followed immediately by 4 cycles of blinatumomab. Patients will be stratified by whether they have minimal residual disease at baseline. Study endpoints include event-free survival and absence of minimal residual disease.

Eunice S. Wang, MD An important consideration for evaluating combinations of these agents for relapsed or refractory ALL will be their sequencing. It will be important to establish whether cytotoxic chemotherapy should be administered first, followed by the immunotherapy, or vice versa. It is possible that immunotherapy may be more effective in patients resistant to or unable to tolerate high doses of chemotherapy.

Elias J. Jabbour, MD The approved and emerging agents for salvage therapy are associated with reasonable—even good—responses. Unfortunately, these responses tend to not be very durable. Potentially, by initiating immunotherapies earlier in the natural course of the disease, more durable responses may be achievable. It is possible that in the future, CAR T-cell therapy will find itself in the frontline management of ALL.

Eunice S. Wang, MD Yes, exactly. Multiple cycles of hyper-CVAD chemotherapy seem to be effective, but not curative; the patients do experience relapse. These patients typically experience immunosuppression, specifically, myelosuppression. Patients may emerge from these chemotherapy cycles with a response, but their immune system has taken a beating. If the patients then undergo salvage immunotherapy, the immune system is unable to mount a strong response, and treatment benefits are unlikely to last long. Responses to immunotherapies used in the salvage setting (ie, after cytotoxic chemotherapy) are typically limited to 6 months or less. A critical question is whether better responses are possible if immunotherapy is used in the upfront setting before the patient's immune system is ablated by highly cytotoxic chemotherapy.

Elias J. Jabbour, MD Earlier use of immunotherapy may minimize or postpone the need for cytotoxic chemotherapy and all of its associated toxicities.

Eunice S. Wang, MD The newer classes of immune checkpoint inhibitors have shown promising activity in patients with solid tumors, who typically do not experience the same degree of myelosuppression from cytotoxic chemotherapy. These patients achieve good responses that appear to be durable.

Elias J. Jabbour, MD You raise an interesting issue. What is known about the immune checkpoint inhibitors in ALL?

Eunice S. Wang, MD It is an interesting area of investigation. Although immune checkpoint inhibitor therapy in other lymphoproliferative disorders, such as refractory or relapsed Hodgkin lymphoma, have been associated with response rates as high as 87%,[28] the efficacy of these approaches in ALL remains to be determined. In addition, although these agents are highly beneficial in a subset of patients, many patients do not respond or inevitably relapse, raising the questions of how to identify those individuals most likely to respond to these approaches and how to convert these immunotherapeutic responses into the same sort of durable remissions that can be achieved after stem cell transplant.

Dan Douer, MD Although disease progression and the development of relapsed or refractory ALL remain significant issues, it is important to consider that our ability to address this disease in the salvage setting has advanced greatly in recent years. First, the availability of vincristine sulfate liposome injection is significant because of its broad applicability in both B-lineage and T-lineage ALL. Secondly, mounting evidence suggests that immunotherapy will have an important role in the treatment of this disease. Although it seems that we are now able to achieve second, third, and fourth remissions in patients with ALL, these remissions are inherently very short.

Moving these agents into the frontline setting may be an important strategy to improve overall patient outcomes. For example, replacing traditional vincristine with vincristine sulfate liposome injection in frontline chemotherapy regimens may permit administration of higher cumulative

doses of vincristine. As previously discussed, incorporating immunotherapy into the frontline management of ALL may increase efficacy because the patient's immune system is in a stronger, more robust state before the occurrence of myelosuppression related to cytotoxic chemotherapy.

Overall, preventing relapse should be the ultimate goal in ALL disease control. Avoiding stem cell transplant, with its potentially serious adverse events, is also important. Moving immunotherapies into the frontline setting has the potential to overcome persistence of minimal residual disease without relying so heavily on stem cell transplant.

Another major gap in the treatment of ALL is the lack of small molecules available for the treatment of Ph-negative ALL. There are far more small-molecule agents in clinical development for the treatment of acute myeloid leukemia, with many agents, including the FLT3 inhibitors, under investigation across multiple classes.

An ongoing phase 1, dose-escalation/dose-expansion trial is investigating the novel spleen tyrosine kinase (Syk) inhibitor entospletinib.[29] The Syk pathway is an apoptotic regulator of several cell-signaling pathways important in B-cell–lineage ALL cells, including PI3K/Akt, NFκB, and STAT3.[30] It is proposed that inhibition of the Syk pathway in ALL patients has the potential to relieve the apoptotic inhibition notorious in these cells. This clinical trial is evaluating entospletinib in combination with vincristine (the traditional formulation, not vincristine sulfate liposome injection) and dexamethasone for the treatment of adults with relapsed or refractory ALL. In animal models, it seemed that the combination of these agents showed a synergistic effect.

Disclosure

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

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A Man With CD10-Positive, CD34-Positive B-Cell ALL

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Case Description

A 27-year-old man presented to the clinic in 2014 with fatigue and flu-like symptoms. He was diagnosed with thrombocytopenia (26,000 platelets/mm^3) and anemia (hemoglobin level of 6 g/dL). A bone marrow biopsy revealed pre–B-cell ALL with a 90% blast count. Immunophenotyping demonstrated that he was CD10-positive and CD34-positive, consistent with an early progenitor B-cell ALL. At the time of the initial diagnosis, the patient's sister was identified as an HLA match, and her stem cells were frozen for future stem cell transplant.

The patient underwent induction therapy with 6 cycles of a fractionated hyper-CVAD regimen (consisting of cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine.[1] He achieved a CR but had evidence of minimal residual disease by flow cytometry following completion of his induction regimen. Unfortunately, just prior to planned stem cell transplant, and approximately 4 months after completing induction, he was found to have circulating blasts consistent with disease relapse. This finding was confirmed by subsequent bone marrow biopsy. He then underwent reinduction therapy with the pediatric-inspired CALGB 10403 protocol, a recently completed, multicenter, phase 2 study for the treatment of Ph-negative ALL patients ages 16 to 39 years.[2] The CALGB 10403 protocol consists of a 4-drug induction regimen including intrathecal cytarabine and intrathecal methotrexate, followed by consolidation, interim maintenance, delayed intensification, long-term maintenance (2 to 3 years), and radiotherapy (for patients with testicular or central nervous system disease or with T-cell ALL). Unfortunately, the patient's ALL was refractory to the CALGB 10403 regimen, with persistent leukemic blasts in his bone marrow.

At this point, because his leukemia cells expressed CD19, arrangements were made for him to be enrolled in a clinical trial of CD19-positive CAR T-cell therapy. However, given the presence of 30% blasts in his marrow, it was evident that his tumor burden had to be reduced while he awaited reinfusion of the genetically modified T cells. He received vincristine sulfate liposome injection combined with prednisone.[3] After his first dose, he complained of arthralgia, myalgia, and jaw pain. However, he was still functional, and he continued treatment with vincristine sulfate liposome injection administered as outpatient therapy. The patient's cell counts stabilized. Marrow restaging immediately prior to CAR T-cell infusion showed a reduction in the blast count to just 2%, consistent with a marked response to vincristine sulfate liposome injection.

The patient received 2 infusions of genetically modified T cells, because a bone marrow biopsy performed after the first infusion continued to show persistent disease. After the second infusion, he developed an overt relapse, with a 60% marrow blast count. Corticosteroids were administered with no effect. The patient's marrow blasts increased to 85%. Because the disease was still CD19-positive, the patient initiated therapy with blinatumomab. However, within 10 days of beginning the blinatumomab cycle, he experienced further disease progression and was deemed unresponsive to blinatumomab. He became progressively ill with active tumor lysis, hypercalcemia, and hyperleukocytosis. Next, he underwent another reinduction chemotherapy regimen with fludarabine, cytarabine, idarubicin, and filgrastim (FLAG-IDA). Unfortunately, his disease proved to be refractory to this regimen as well. Three weeks later, his bone marrow still exhibited a blast count of 50%.

At this point, the patient was generally deconditioned and weak. We were unsure if he would be able to tolerate any other aggressive multiagent cytotoxic chemotherapy. We reviewed his treatment history and found only one drug that had achieved a response: vincristine sulfate liposome injection. We therefore made the decision to administer another dose of vincristine sulfate liposome injection 3 weeks after his failure of FLAG-IDA. After 1 dose, he showed a significant cytoreduction in his bone

Table 2. CR/CRi According to Subgroups in a Phase 2 Trial of Vincristine Sulfate Liposome Injection

Subgroup	Patients (n)	%
Relapsed ALL	9	25
Relapsed/refractory ALL	4	14
Vincristine sulfate liposome injection line of therapy		
Third-line	6	19
Fourth-line	5	21
Fifth-line or greater	2	22
Prior HCT	8	26
No prior HCT	5	15
Prior clofarabine treatment		
In a multidrug regimen	0	0
As a single agent	2	50
No prior clofarabine treatment	11	19

CR, complete response; CRi, complete response with incomplete hematologic recovery; HCT, hematopoietic cell transplantation.

Adapted from O'Brien S et al. *J Clin Oncol*. 2013;31(6):676-683.[3]

marrow blasts, from 50% to 5%. This round of vincristine sulfate liposome injection was associated with slightly more myalgia and arthralgia, as well as severe, persistent constipation. He subsequently received inotuzumab ozogamicin on a compassionate exemption protocol. After his first cycle of treatment, the patient achieved a morphologic CR with evidence of minimal residual disease by flow cytometry and B-cell clonality assays. Currently, he is awaiting allogeneic stem cell transplant using the frozen cells from his HLA-matched sibling.

Case Discussion

Eunice S. Wang, MD An important point highlighted by this case is that vincristine sulfate liposome injection was associated with a great deal of efficacy even in a setting in which the more targeted immunotherapies did not seem to be as beneficial. We treated the patient with vincristine sulfate liposome injection on 2 separate occasions, and both times he achieved a marked cytoreduction (Table 2). Notably, both times the vincristine sulfate liposome injection was administered with the goal of bridging—first to CAR T-cell therapy and second to allogeneic stem cell transplant. Both times, we were able to achieve this goal. Overall, vincristine sulfate liposome injection was well-tolerated. The toxicities were slightly more bothersome with the second administration, perhaps because the patient's overall health was in a worsened state as opposed to during the first course of treatment.

Elias J. Jabbour, MD This interesting case illustrates the potential for administering blinatumomab and inotuzumab ozogamicin earlier in the treatment course. This patient had a particularly aggressive form of ALL, and it is becoming apparent that the greater the patient's disease burden, the lower the response to these agents.

Eunice S. Wang, MD Yes, I agree. In retrospect, it could be suggested that giving the blinatumomab so soon after the CAR T-cell therapy, especially in light of this patient's high disease activity, was not ideal. However, at that point, we were trying to avoid even more cytotoxic chemotherapy, which had the potential to abolish any potential benefit the CAR T cells may have had. In fact, this scenario likely transpired when we gave him the FLAG-IDA regimen.

Although vincristine sulfate liposome injection should probably not be seen as a curative therapy, it appears to fill an important gap for patients who require disease control but do not respond to immunotherapies and/or are refractory to available cytoreductive chemotherapy regimens.

Disclosure

Dr Wang has served on advisory boards for Sigma Tau and Spectrum Pharmaceuticals. She is on the speakers bureau for Incyte.

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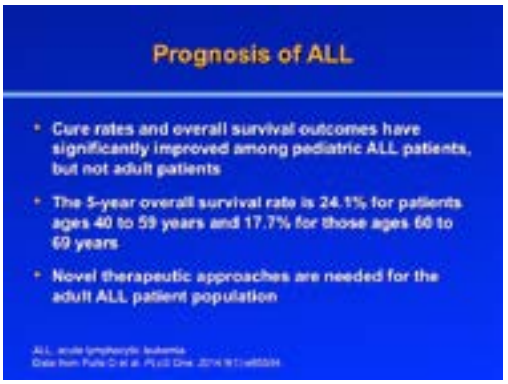

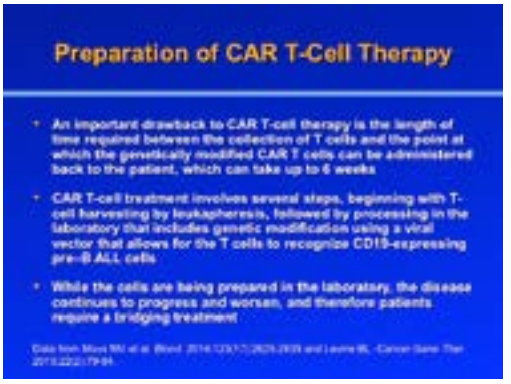

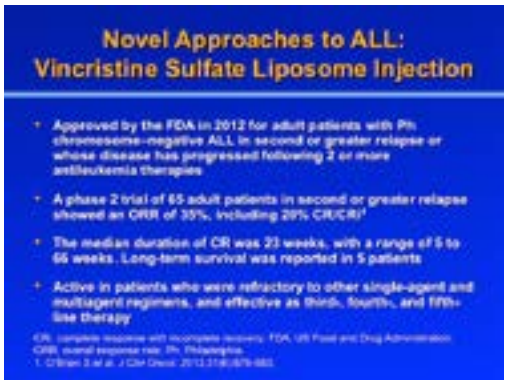

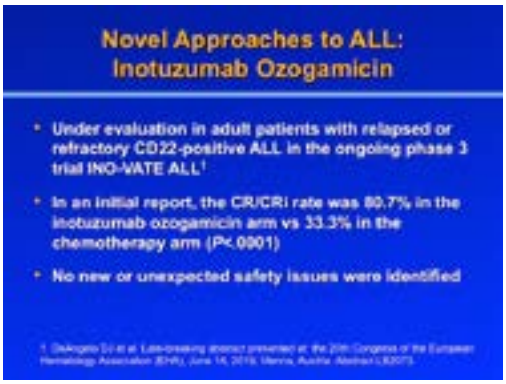

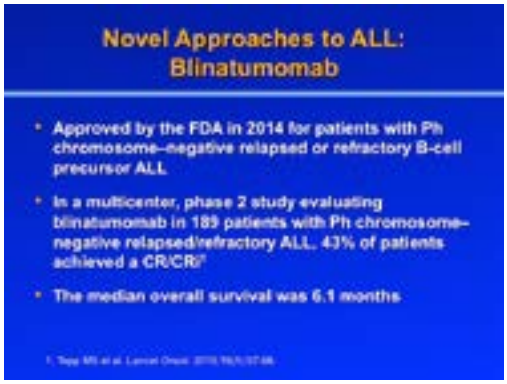

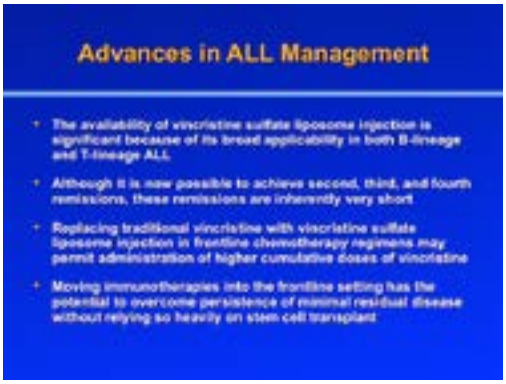

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