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Novel Management Options for Adult Patients With Progressive Acute Lymphoblastic Leukemia: A Case-Study Compendium

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Abstract: Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by highly proliferative immature lymphoid cells in the bone marrow and peripheral blood. In adults, ALL accounts for approximately 20% of all adult leukemias. ALL carries a poor prognosis in adults. The 5-year overall survival is 24% in patients ages 40 to 59 years and 18% in patients ages 60 to 69 years. ALL can be grouped into different categories according to its cell lineage (B cell or T cell), the presence or absence of the Philadelphia chromosome, and various cytogenetic and molecular classifications. A main goal of treatment is to allow the patient to achieve a complete remission and to consolidate this remission with either a maintenance regimen or an allogeneic stem cell transplant. Although the overall rate of complete remission following frontline therapy for newly diagnosed ALL is high, the majority of patients experience a disease relapse. In general, the duration of initial complete remission impacts the patient's prognosis and response to further therapies. Subsequent treatments must balance the goal of achieving a remission with the need for the patient to maintain or improve quality of life. Recently approved agents, such as blinatumomab and vincristine sulfate liposome injection, offer the promise of a second remission that can serve as a bridge to allogeneic stem cell transplant while still maintaining quality of life. A novel approach using adoptive cellular immunotherapy with chimeric antigen receptor (CAR) T cells is associated with extremely robust responses.

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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

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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 Management Options for Adult Patients With Progressive Acute Lymphoblastic Leukemia: Introduction

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Acute lymphoblastic leukemia (ALL) is a heterogeneous clonal malignancy, characterized by the overproliferation of immature lymphoid cells of either T-cell or B-cell lineage. This proliferation occurs in both the peripheral blood and the bone marrow. In adults, approximately 75% of cases involve B-cell lineage cells, and 25% involve T-cell lineage cells.[1,2] Involvement of the central nervous system, lymph nodes, spleen, liver, and gonads can also occur. In 2014, the total estimated number of new ALL cases in the United States was 6020.[3] ALL is the most common pediatric malignancy, with 60% of cases occurring in patients younger than 20 years.[4]

There are several prognostic categories of ALL based on factors such as the initial presenting white blood cell count, the immunophenotype, cytogenetics, mutations, and the presence or absence of minimal residual disease (MRD) after the first cycle of chemotherapy. There are many regimens for the upfront treatment of ALL with no universally accepted standard of care. Nearly all management approaches involve alternating cytotoxic chemotherapy drugs, given over defined intervals, with the aim of avoiding cross resistance.

Approximately half of patients will develop relapsed and/or refractory disease. Refractory ALL is defined as failure to achieve a complete remission (CR) with standard induction chemotherapy. Relapsed ALL is defined as the reappearance of ALL cells in the bone marrow or peripheral blood after a CR. In general, up to 90% of adult patients with ALL will achieve a CR after frontline induction chemotherapy.[4] However, the overall survival rates remain low. Relapse will occur in approximately two-thirds of patients with high-risk ALL and one-third of patients at standard risk.

The ideal salvage regimen for patients with relapsed/refractory Philadelphia (Ph) chromosome–negative ALL has not been established. Until now, the most commonly utilized therapy for patients with relapsed/refractory B-cell ALL consisted of readministration of multiagent cytotoxic drugs. In general, therapy depends upon the timing of relapse. If relapse occurs more than 2 years following initial treatment, then reinduction with a regimen similar to that used upfront may be effective. In contrast, patients with primary resistant disease or whose disease recurs during initial induction, consolidation, or maintenance therapy should ideally be retreated with a novel regimen or biologic agents. A commonly employed regimen in this setting is the fludarabine, high-dose cytarabine, and granulocyte-colony stimulating factor (FLAG) regimen.[5] Although many patients can achieve a second remission with this approach, overall remission durations are generally not durable, lasting less than 1 year. Therefore, whenever possible, patients in second remission should proceed as soon as possible to an allogeneic stem cell transplant, which offers the only chance for long-term cure. In clinical practice, however, this goal is often not met, either because a second complete remission is not achieved, or the patient develops comorbidities that preclude transplantation.

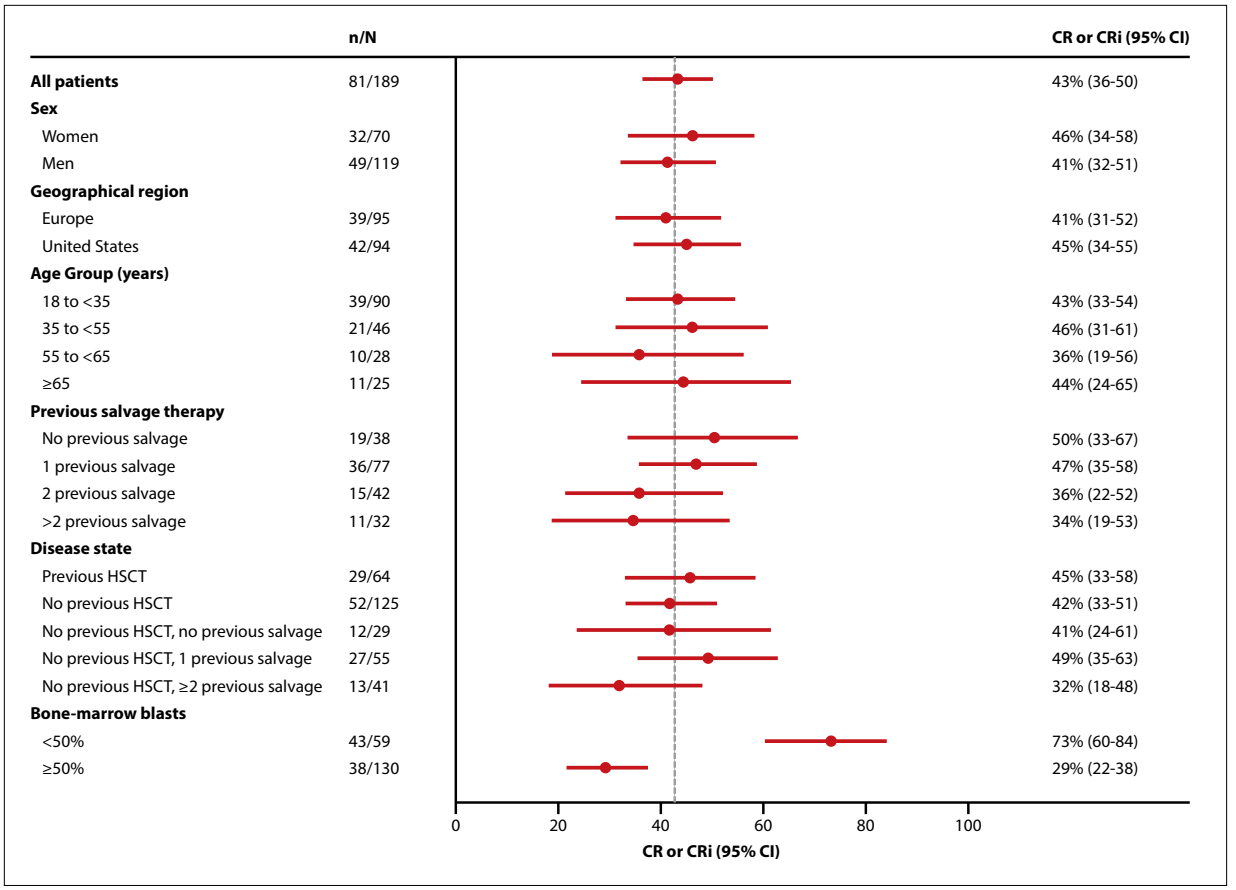

Figure 1. Overall response according to subgroup among patients receiving blinatumomab in a multicenter, phase 2 study of 189 patients with Ph chromosome–negative relapsed/refractory ALL. CR, complete response; CRi, complete response with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant. Adapted from Topp MS et al. *Lancet Oncol*. 2015;16(1):57-66.[12]

Two nucleoside analogues chemotherapy agents have recently been developed for the treatment of specific subsets of relapsed ALL patients. Clofarabine is a nucleoside analogue approved for single-agent use in pediatric patients younger than 21 years with second or greater disease relapse.[6] This agent has also been employed off-label in adult ALL patients,[6] based in part on phase 1 and 2 clinical trials demonstrating a complete remission rate of 12% to 17% in older patients and an overall response rate of 20%. Toxicities of this drug include nausea, vomiting, myelosuppression, fever, rash, and elevated liver function test results.[7-9] Nelarabine is another purine nucleoside agent with T-cell specific action similar to cytarabine. It is indicated for the therapy of relapsed/refractory T-cell ALL patients after at least 2 prior therapies. Small studies in both pediatric and adult ALL patients demonstrated a modest overall response rate of approximately 20% to 23%. In a larger trial involving adult patients with relapsed T-cell ALL, 45 of 126 evaluable patients (36%) achieved CR. One-year survival after treatment, however, was only 24%, and the treatment was associated with significant risks of drug-related myelosuppression and neurotoxicity.[10] Notably, the majority (80%) of patients achieving CR were able to proceed to transplant, with almost one-third of these patients (31%) still alive at 3 years.

At present, the most exciting approaches for relapsed ALL involve immunotherapeutic agents capable of harnessing the patient's own immune system to eradicate disease. Blinatumomab is a bispecific antibody binding both CD19 expressed by B-cell ALL cells and CD3 expressed on host T cells. The activity of this agent lies in its ability to act as a specific T-cell engager activating endogenous host T cells to recognize and bind to the CD19-expressing target cell. By bringing T cells into close proximity with CD19-positive ALL B cells, the host T cells are stimulated to recognize and destroy tumor cells. Blinatumomab was granted accelerated approval in December 2014 for the treatment of patients with Ph chromosome–negative relapsed or refractory B-cell precursor ALL. This approval was based on results from an initial phase 2 trial reporting that more than two-thirds

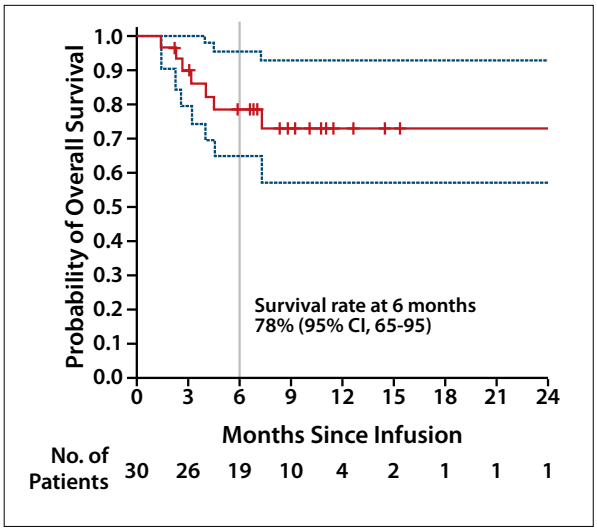

Figure 2. Overall survival among adults and children with relapsed or refractory ALL receiving chimeric antigen receptor-modified T-cell therapy in a single-arm, phase 2 trial. The blue lines show the 95% confidence intervals. The tick marks show the time of data censoring at the last follow-up or when alternative therapy was initiated. Adapted from Maude SL et al. *N Engl J Med*. 2014;371(16):1507-1517.[13]

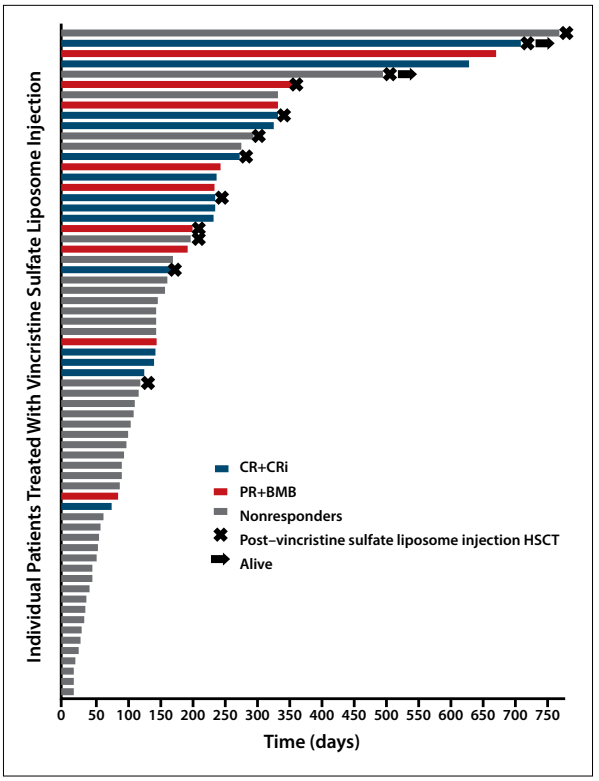

Figure 3. Overall survival and HSCT among patients treated with vincristine sulfate liposome injection in a phase 2 trial. BMB, bone marrow blast response; CR, complete response; CRi, complete response with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; PR, partial remission. Adapted from O'Brien S et al. *J Clin Oncol*. 2013;31(6):676-683.[14]

(69%) of relapsed B-cell ALL patients treated with blinatumomab achieved either a CR or a CR with a partial hematologic recovery (CRi).[11] Elimination of MRD was achieved in 88% of patients, with approximately half of the responding patients undergoing subsequent stem cell transplant. The final results of blinatumomab therapy in a large, multicenter, phase 2 study of 189 patients with Ph chromosome–negative relapsed/refractory ALL were recently reported.[12] Patients were enrolled in several different dose cohorts. Their median age was 39 years. Almost 40% (74 patients) had received 2 or more prior lines of salvage therapy, and one-third had undergone a previous allogeneic stem cell transplant. Of note, more than two-thirds of patients had at least 50% bone marrow blasts at initiation of therapy. After 2 blinatumomab cycles, 43% of patients achieved a CR (33%) or CRi (10%). Among the responding patients, 40% proceeded to allogeneic stem cell transplant. Of note, responses were seen in patients older than 65 years (44%), as well as in patients who had previously undergone allogeneic stem cell transplant (45%; Figure 1). However, the median overall survival was still fairly short at 6.1 months, supporting the fact that responses were not durable and that additional treatment will be warranted for those patients not eligible for subsequent transplant.[12]

Harnessing the patient's own immune system via engineering of chimeric antigen receptor (CAR) T cells from autologous cells constitutes perhaps the most groundbreaking approach for the treatment of relapsed ALL. With this procedure, the patient's own T cells are collected by apheresis procedures, expanded ex vivo in the laboratory, and subsequently genetically altered using retroviral technology (similar to HIV infection by viruses) to recognize and attack CD19-positive B-cell ALL cells. CAR T cells are also engineered to express signaling pathways leading to constitutive activation and expansion in vivo and therefore may represent an alternative means of cellular immunotherapy similar to allogeneic stem cell transplant. To date, CAR T-cell therapy has been limited to only a few centers with the ability to safely generate and infuse these modified T cells. However, to date, this approach has been associated with the highest rates of complete remission achieved in any relapsed ALL population, in the range of 80% to 90%. In the largest published trial, 30 children and adults with relapsed/refractory B-cell ALL received CAR T cells at the University of Pennsylvania. Complete remission was achieved in 27 patients (90%), including 2 patients who had blinatumomab-refractory disease.[13] Moreover, many of these responses proved durable, with a 6-month event-free survival rate of 67% and an overall survival rate of 78% (Figure 2).[13]

Although most of the above therapies for relapsed/refractory ALL are limited to specific disease subsets based on clinical characteristics (pediatric vs adult patients) and/or immunophenotype (T-cell vs CD19-positive B-cell ALL), treatment with another agent, vincristine sulfate liposome injection, offers the potential for therapeutic benefit across all relapsed ALL patients. This agent was designed to encapsulate vincristine (a water-soluble drug) in a liposomal covering, thereby radically changing the drug's pharmacokinetics and allowing much higher doses of vincristine to be administered as a single agent. Liposomal vincristine is currently approved for the treatment of adult patients with Ph chromosome–negative ALL in second or greater relapse or whose disease has progressed following 2 or more antileukemia therapies. In the pivotal phase 2 study leading to its approval, vincristine sulfate liposome injection was administered to 65 adult patients in second or greater relapse.[14] All of the patients had received prior vincristine as part of their frontline chemotherapy. The rate of CR and CRi was 20%, and the overall response rate was 35% (Figure 3). The median duration of complete remission was 23 weeks (range, 5-66 weeks). Five patients achieved long-term survival. Moreover, single-agent vincristine sulfate liposome injection was effective as third-, fourth-, and fifth-line therapy, and was active in patients who were refractory to other single-agent and multiagent regimens. Importantly, several patients who responded to vincristine sulfate liposome injection had very poor performance status and were therefore not candidates for other toxic salvage chemotherapy regimens, stem cell transplantation, or a clinical trial with a novel immunotherapeutic agent. Achievement of clinical response to vincristine sulfate liposome injection served as a successful bridge to stem cell transplant in 12 patients. Neurotoxicity was the primary adverse event.

In summary, a multitude of options are available for the treatment of relapsed/refractory ALL patients. The appropriate use and application of these therapies are illustrated in the following case scenarios.

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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An ALL Patient With a t(4;11) Translocation

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Case Description

A 50-year-old woman presented to her primary care physician after experiencing some shortness of breath at exertion. A blood test revealed pancytopenia, and the patient was referred to a hematologist at the MD Anderson Cancer Center. A bone marrow aspiration and biopsy showed that the patient had pre–B-cell ALL that was CD20-positive. Chromosome testing did not show a t(9;22) translocation, and the patient was therefore Ph chromosome–negative. She did, however, have a t(4;11) translocation within the *MLL* gene rearrangement.

The patient began induction treatment with rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with a high-dose methotrexate and cytarabine regimen, given with intrathecal cytarabine and methotrexate therapy. She achieved a CR after just the first cycle of therapy; however, she remained MRD-positive by multicolor flow cytometry. The patient experienced no side effects of concern.

Due to the poor prognosis associated with the t(4;11) translocation present in her disease, she was referred to the stem cell department to discuss the possibility of an allogeneic stem cell transplant. The patient was hesitant to move forward with this procedure and instead elected to continue with her chemotherapy treatments. However, even after receiving 3 more cycles of chemotherapy, she remained MRD-positive. Alarmed, her hematologist again recommended that she undergo a stem cell transplant, to which she ultimately agreed. Unfortunately, her disease returned before she could undergo transplant.

The patient was then enrolled on a clinical trial of blinatumomab. She was also receiving intrathecal therapy to prevent central nervous system relapse. The patient received 2 cycles of blinatumomab, with no response to treatment. A bone marrow biopsy performed at study entry and after 2 cycles found no change in her blast count of 90%. Immediately after each treatment, she experienced slight fever and tremor, but they resolved quickly. She stopped blinatumomab, and was taken off the study.

The patient then received FLAG and idarubicin (IDA) in combination with vincristine sulfate liposome injection. The patient became MRD-negative for the first time. She did, however, experience significant myelosuppression, which persisted for approximately 45 days.

At this point, she was ready to proceed to her stem cell transplant from an unrelated donor. Posttransplant, she had acute graft-vs-host disease (GVHD) involving her skin and gastrointestinal tract. This reaction was managed relatively effectively with tacrolimus and a corticosteroid. Her most current assessment, performed at day 100 posttransplant, showed that she was still MRD-negative and that her platelet count had recovered to 75,000 cells/mm^3.

Case Discussion

Dan Douer, MD The fact that the addition of vincristine sulfate liposome injection to FLAG-IDA resulted in a conversion to MRD-negative status in the patient is quite impressive, especially given her particularly unfavorable prognosis. The t(4;11) translocation, occurring within the *MLL* gene, is found in approximately 10% of newly diagnosed adult patients with B-cell ALL (Table 1).[1] This translocation is associated with a poor prognosis, as is a short duration of response to frontline treatment.[2,3] Because this patient exhibited both of these factors, it is remarkable that she was able to achieve MRD-negativity.

Eunice S. Wang, MD Is it a common approach at your institution to combine vincristine sulfate liposome injection with the FLAG-IDA regimen? I have not previously seen data for this specific combination approach.

Elias J. Jabbour, MD It is not a standard of care, but it is becoming more widely used in our center. Typically, the vincristine sulfate liposome injection is given at days 4 and 11 of the FLAG-IDA cycle, and the maximum dose is 4 mg/m^2. In our experience, this combination can be given successfully with no additional myelosuppression. There have been some instances of peripheral neuropathy. However, this patient had not experienced any peripheral neuropathy with her initial hyper-CVAD regimen, which contained vincristine, and we therefore had some

Table 1. Cytogenetic Molecular Classification of Adult ALL

Risk Group	Chromosomal/Molecular Aberrations	5-Year DFS (%)	5-Year OS (%)
Standard risk	Isolated 9p/p15-p16 deletions High hyperdiploidy Normal karyotype/no molecular aberrations	35-68	48-80
Intermediate risk	del(6q) Trisomy of chromosome 21 Trisomy of chromosome 8 t(1;19)/*E2A-PBX*	37-51	35-40
High risk	t(9;22)/*BCR-ABL* t(4;11)/*MLL-AF4* 11q23 MLL rearrangements Monosomy of chromosome 7 Low hypodiploidy/near triploidy Complex karyotype High *BAALC* expression Aberrations of *IKZG1* gene	10-52	15-35

ALL, acute lymphoblastic leukemia; DFS, disease-free survival; OS, overall survival.

Adapted from Marchesi F et al. *Adv Hematology*. 2011;2011: Article ID 621627.[1]

confidence that she would do well with the FLAG-IDA plus vincristine sulfate liposome injection combination.

Eunice S. Wang, MD In our center, we have substituted vincristine sulfate liposome injection for standard vincristine in the cyclophosphamide, vincristine, and prednisone regimen with some success. What other cytotoxic chemotherapy agents have you successfully combined with vincristine sulfate liposome injection?

Elias J. Jabbour, MD We have used several approaches, although it should be emphasized that none are considered a standard of care. We have found that, in general, vincristine sulfate liposome injection combines well with other therapies, without causing an increase in significant myelosuppression or neuropathy. For example, clofarabine, which is approved for the treatment of pediatric relapsed/refractory ALL, is effective when combined with vincristine sulfate liposome injection. We have also found that vincristine sulfate liposome injection can be combined with bortezomib in patients with double-hit B-cell ALL.

The combination of vincristine sulfate liposome injection with hyper-CVAD is currently being tested in a nonrandomized phase 2 clinical trial.[4] In this study, the combination is being administered as frontline treatment for newly diagnosed ALL in adults. The regimen also includes rituximab for patients with CD20-positive disease, and/or imatinib or dasatinib for patients with Ph chromosome–positive disease. The primary endpoint of this study is the rate of CR at 1 year.

Disclosure

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

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An ALL Patient With Heart Failure

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Case Description

A 60-year-old woman presented with fever and abdominal pain. She was found to have an enlarged spleen. A complete blood count with differential showed that her white blood cell count was 80,000 cells/mm^3, nearly all of which were lymphoblasts. A flow cytometry analysis confirmed that she had pre–B-cell ALL that was positive for terminal deoxynucleotidyl transferase and expressed the CD10, CD19, and CD20 antigens. No abnormal karyotype was detected, and she was negative for the Ph chromosome.

The patient's health history was significant for hypertension and chronic obstructive pulmonary disease. Two years earlier, she had experienced a myocardial infarction, which left her with a left ventricular ejection fraction of only 50%. Overall, she had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Given her health history, it was clear that she would not be a good candidate for a clinical trial.

Although the patient and her family felt strongly about beginning treatment, they were hesitant to have her receive very intensive therapy. With no standard of care recommended for her age and performance status, the patient was treated with a chemotherapy course modeled after the Medical Research Council United Kingdom Acute Lymphoblastic Leukaemia Trial XII/ECOG 2993 regimen, except the pegaspargase was removed because of its toxicity for her age group. Therefore, her first phase of induction consisted of daunorubicin, vincristine, and prednisone, and her second induction phase consisted of cyclophosphamide, cytarabine, and 6-mercaptopurine. She achieved a CR and became MRD-negative. However, because of her overall health status, it was decided that she would not undergo stem cell transplant.

She subsequently experienced a disease relapse 8 months later. She was then treated with intermediate doses of methotrexate and cytarabine, which resulted in a short remission. Although the plan was to begin treatment with blinatumomab, the patient developed heart failure, and her left ventricular ejection fraction dropped to 35%. The symptoms of hypertension and hypoxia that can occur with blinatumomab can usually be managed with corticosteroids. Given this patient's state of health, however, it was thought that the associated risks were too high. In addition, the median survival of patients treated with blinatumomab is only approximately 6 months.

The exclusion of blinatumomab prompted consideration of other treatment options. We considered use of an experimental agent, the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin, but we were uncertain of whether this agent would achieve a response. The patient had tolerated her previous exposure to standard vincristine relatively well, with only an absence of tendon reflexes, and no numbness. Therefore, she was given vincristine sulfate liposome injection.

After her first 3 doses, she experienced neuropathy and muscle cramps that were bothersome but not severe. Consequently, her dose interval was increased from 7 days to 10 days, which improved the neuropathy. She again achieved a CR and became MRD-negative. Her cardiac condition remained stable, and she had no hemodynamic complications. In fact, her quality of life improved significantly during this time, likely due to the remission. Treatment was continued for approximately 2.5 months, until she experienced a disease relapse. At that point, the decision was made for her to enter hospice. She died shortly thereafter.

Case Discussion

Dan Douer, MD Vincristine sulfate liposome injection was a good option for this patient, not only because of its response rate, but also because it is relatively easy to administer. It was given once a week by her oncologist in the community, allowing her to stay with her family. As previously discussed, vincristine sulfate liposome injection is associated with a CR rate of 20% and an overall response rate of 35%.[1] The median duration of survival is approximately 4.6 months, although it is slightly higher in responding patients. Maintaining her quality of life for this duration of time was reasonable and in line with the wishes of the patient and her family. She received vincristine sulfate liposome injection at a standard dose of 2.25 mg/m^2.

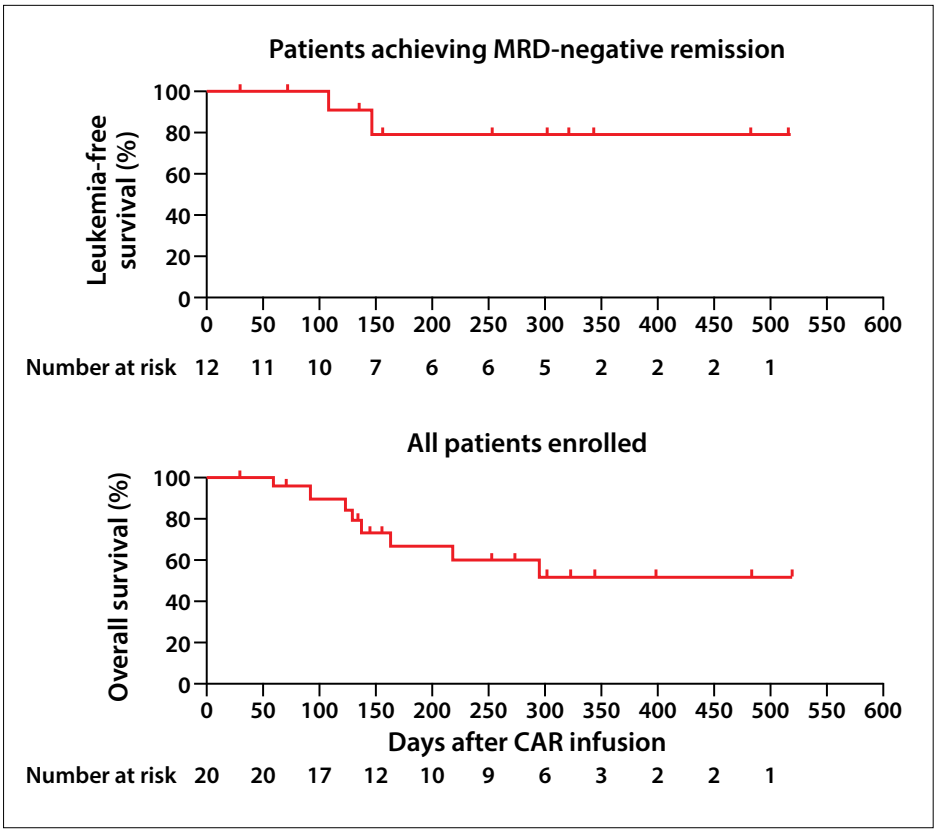

Figure 4. Survival in a study of children and young adults with ALL receiving CAR T-cell therapy. ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; MRD, minimal residual disease. Adapted from Lee DW et al. *Lancet*. 2015;385(9967):517-528.[2]

Elias J. Jabbour, MD Are there any recommendations for maintenance therapy posttransplant for patients who relapse multiple times?

Dan Douer, MD There are no good recommendations for this setting, especially if we want to avoid cytotoxic chemotherapy agents. One potential strategy is the use of autologous CAR T cells. This novel technology, described above, is still experimental. It shows great promise in relapsed pre–B-cell ALL, although it has not been studied in patients who have undergone allogeneic transplant. Since the autologous CAR T cells remain active for many months—and possibly, years—they may be considered a maintenance strategy. The interaction with the grafted T cells must be studied.

Elias J. Jabbour, MD Is there a role for CAR T cells earlier in the treatment of ALL, perhaps in combination with minimal chemotherapy?

Dan Douer, MD This is an interesting question. Thus far, the data supporting CAR T-cell therapy in ALL has come from patients with relapsed disease. In pediatric ALL patients, CAR T-cell therapy can result in very long remissions and possibly a cure (Figure 4).[2] We do not yet know if very long remissions can be obtained in adults.

Another question concerns the activity of CAR T cells in patients with newly diagnosed ALL who respond to frontline induction combination chemotherapy but remain MRD-positive, either prior to stem cell transplant or even as a replacement for transplant. The toxicity of CAR T cells will be less severe in patients with minimal disease than in patients with overt relapse. It would be especially exciting if CAR T cells used in this early setting could be a curative strategy and replace allogeneic stem cell transplant. The use of autologous CAR T cells would mean that patients would no longer be enduring GVHD. I would not be surprised if, in the future, CAR T-cell therapy will be an alternative strategy to transplant, at least for some patients, after induction chemotherapy.

The same question could be asked regarding the potential role of blinatumomab as part of frontline therapy. An ongoing phase 3 clinical study (ECOG-American College of Radiology Imaging Network [ACRIN] E1910) is currently open and evaluating this question. Patients ages 35 to 70 years with Ph chromosome–negative pre–B-cell

ALL will first receive 3 cycles of chemotherapy.[3] After the third cycle, they will be randomized to either continue with consolidation and maintenance chemotherapy or instead receive 4 cycles of blinatumomab and then continue with the same consolidation and maintenance chemotherapy. Both MRD-positive and MRD-negative patients are being enrolled, but the study is powered with the idea that the treatment effect will be observed primarily in MRD-positive patients.

Eunice S. Wang, MD How do you think the risks of stem cell transplant compare with the potentially life-threatening cytokine release syndrome (CRS) that occurs with CAR T-cell therapy, especially for a patient, such as the one in this case, who could not tolerate intensive chemotherapy. Do you think she would have been able to tolerate CAR T-cell therapy?

Dan Douer, MD This is an important question since the toxicities of CAR T cells and allogeneic transplant are very different. The toxicity of allogeneic transplant is caused by the pretransplant conditioning regimens. More importantly, acute or chronic GVHD can be severe, persistent, and occasionally debilitating. Patients undergoing transplant are required to have normal organ function, including heart function. Therefore, patients with heart disease, such as this patient, would not be offered this treatment.

CAR T-cell therapy avoids the problem of GVHD, but it can cause CRS. The toxicity associated with CRS is of a short duration and occurs during the first 2 weeks after infusion of the cells. The severity of CRS can vary and is related to higher tumor burden. CRS symptoms would be milder, primarily limited to fever, in patients who have already achieved MRD-negative status. Severe CRS can manifest as hypotension or hypoxia, and often requires the hemodynamic and respiratory support of an intensive care unit. With this consideration in mind, the risk of fatal CRS in this patient with heart failure was prohibitive. CAR T-cell therapy may also be associated with neurologic side effects, mainly seizures and altered mental status, which may not be related to the CRS.

In MRD-negative patients, CAR T-cell treatment would be preferred to transplant because mild CRS is a safer outcome than GVHD. In patients with heart failure, however, CAR T-cell therapy would not be a good option. Future research may mitigate the severity of CRS, and patients with heart failure might be able to receive treatment with CAR T-cells. It is possible that in heart failure patients with low disease burden or MRD-negativity, the risk of CRS involved with CAR T-cell therapy could be low enough to make the approach feasible. However, the risk of the hemodynamic complications associated with CRS should be very carefully evaluated when considering the use of CAR T-cell therapy in patients with baseline abnormal heart function, even in the setting of low disease burden.

Eunice S. Wang, MD If a patient is not eligible for transplant, would he or she still be considered eligible for CAR T-cell therapy on the current clinical trials?

Dan Douer, MD Currently, it is not necessary for a patient to achieve a CR before starting CAR T-cell therapy, although the risk of CRS means that some form of tumor reduction is a consideration. In contrast, a CR is a requirement for successful allogeneic transplant. Therefore, patients who do not achieve a CR are not eligible for transplant but can be treated with CAR T cells. A common approach is first to treat with CAR T cells and achieve a CR (rate of 80%-90%) and then follow with allogeneic transplant, which is still considered to have a higher curative potential. Clinical experience demonstrated that transplant can be performed after administration of CAR T cells. Another indication for CAR T cells that excludes use of transplant is the lack of a suitable donor.

Both approaches can be associated with life-threatening toxicities, although as mentioned above, the toxicity profile is different. Therefore, it would be preferable that candidates for both treatment modalities have a good performance status and no severe comorbidities. Since CAR T cells do not cause GVHD, and CRS can be treated with immediate administration of high doses of corticosteroids, it may be a relatively safer approach. However, corticosteroid intervention could interfere with the CAR T-cell activity, and the true effect is not known. The serum level of C-reactive protein is simple to assess, and high levels can be a predictive surrogate of the severity of CRS.

Eunice S. Wang, MD At our institution, we have developed a strategy for patients who are awaiting CAR T-cell therapy. For example, after the patient enrolls in a clinical trial of CAR T-cell therapy, there is often a waiting period of 6 to 8 weeks after the cells have been collected by apheresis, during which time the autologous CAR T cells are genetically altered to express chimeric antigen receptors and expanded to increase cell numbers. In the interim, the patient may have rapidly proliferative ALL disease that needs to be controlled. In addition, because the risk of cytokine release syndrome seems to be directly related to the amount of leukemia tumor burden, we find it useful to give interim chemotherapy in this setting. However, we also do not want to significantly worsen the patient's condition by administering a highly cytotoxic regimen with risks of organ failure and sepsis. In these situations, I have often used vincristine sulfate liposome injection. What options would you consider to bridge these patients while they wait?

Dan Douer, MD We also have used vincristine sulfate liposome injection as a single agent in patients for this exact situation, and it proved to be quite effective. We try to avoid giving corticosteroids, as they could negate the effects of the CAR T cells. Other chemotherapy agents could be used, but the benefit of vincristine sulfate liposome injection is its lower risk of myelosuppression. A CR is not necessary to proceed to CAR T-cell treatment; a partial response (PR) is acceptable. The rate of CR/PR with vincristine sulfate liposome injection is 35% (higher that the 20% CR rate).[1] Although the CR rate associated with vincristine sulfate liposome injection is perhaps not good enough to bridge the patient over to stem cell transplant, the CR/PR rate is good enough to allow the patients to proceed to CAR T-cell therapy.

Eunice S. Wang, MD We have seen cases in which patients receive aggressive clofarabine-based or FLAG-based cytotoxic chemotherapy, and then they either die or they experience severe toxicity that prevents them from proceeding to stem cell transplant or CAR T-cell therapy.

Dan Douer, MD We have been trying to address this same problem. We tend to avoid most forms of chemotherapy, as their toxicities will likely make the subsequent administration of CAR T-cell therapy much more difficult. For this setting, we primarily use single-agent vincristine sulfate liposome injection. For example, one of our patients with active disease and 80% blasts was treated with vincristine sulfate liposome injection, and achieved a good PR. She then went on to CAR T-cell therapy. She developed cytokine release syndrome, but she is 45 years old and otherwise healthy, and she did not require treatment in an intensive care unit.

Elias J. Jabbour, MD There is a question about the availabilities of these therapies. Community physicians may lack practical access to blinatumomab and CAR T cells. Alternatively, single-agent vincristine sulfate liposome injection is very convenient and can be given to these patients.

Dan Douer, MD Blinatumomab requires a continuous intravenous infusion for 28 days, and in the United States, the bags must be changed every 48 hours. An effort has been made for more accessible and widespread use by employing home nurses. However, the challenging logistics of administering blinatumomab in the outpatient setting will still need to be addressed before physicians in every community can use the drug. It is more likely that CAR T-cell therapy will eventually fall within the domain of transplant services, as these procedures share the same basic steps, with the exception that the T cells in CAR treatment are autologous and genetically engineered.

Elias J. Jabbour, MD How does CAR T-cell therapy compare with blinatumomab for use after induction chemotherapy?

Dan Douer, MD In the relapse setting, the activity of the CAR T cells is higher, and the duration of response is longer; the CR rate in active disease is 90%.[4] In contrast, with blinatumomab, the CR rate is 40%.[5] Even if CAR T-cell therapy is approved, it will be limited to centers with the capability to perform the procedure. In contrast, blinatumomab is a drug that can be "taken off the shelf" and would be easier to administer, especially in frontline treatment after induction. This strategy is being evaluated in the ECOG-ACRIN study mentioned above.[3]

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.

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Two Patients With Relapsed/Refractory ALL

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Case Description

A 28-year-old white man was evaluated by his primary care physician for recurrent fevers and chills. His blood work was abnormal, and he underwent a bone marrow biopsy, which demonstrated CD5-positive T-cell ALL with 81% blasts. He did not have a mediastinal mass. He was subsequently referred to our center and admitted to the inpatient service. His white blood cell count at that time was 21,000 cells/mm^3.

A repeat bone marrow biopsy completed at the time of his admission revealed CD3-positive, CD5-positive T-cell ALL with aberrant CD33 myeloid expression. His disease was characterized by a complex karyotype. He was enrolled on the Cancer and Leukemia Group B (CALGB) protocol 10102, consisting of induction chemotherapy with cyclophosphamide, daunorubicin, vincristine, L-asparaginase, and dexamethasone with growth factor support. The patient experienced some complications with this regimen, including prolonged neutropenia and small subdural hematomas. Follow-up bone marrow biopsies demonstrated improvement of the T-cell ALL with 14% blasts. Subsequently, a bone marrow biopsy performed at the time of count recovery demonstrated a CR.

He was then referred to the transplant team, but declined to proceed with transplant despite the fact that he had several 10 out of 10 matched unrelated donors. Per protocol, he was then initiated on early intensification therapy, which consisted of cyclophosphamide, intrathecal methotrexate, cytarabine, and L-asparaginase, with growth factor support. He also received alemtuzumab as part of the original protocol. After completing his seventh course, his bone marrow continued to show morphologic complete remission. He maintained a complete remission for several months. However, several months later, his platelet count dropped precipitously with subsequent bone marrow biopsy confirming relapsed T-cell ALL disease. He then received 4 doses of nelarabine without response with evidence of 74% marrow blasts.

Further treatment options were discussed. We outlined the goal of achieving another CR to allow allogeneic stem cell transplant, given that the patient was young, with excellent performance status, and had several matching unrelated donors. At that time, he was not eligible for blinatumomab or CAR T-cell therapy given his T-cell ALL disease. It was decided that he would receive vincristine sulfate liposome injection. After receiving 4 weekly doses, he achieved a second complete remission and proceeded onto allogeneic transplant. Unfortunately, he died 48 days following transplant of severe complications of acute GVHD.

Case Discussion

Dan Douer, MD A presentation at the 2014 American Society of Hematology meeting showed that early precursor T cells were not different from other types of T cells.[1] I am not certain that this subclassification of T cells is very clear. They may not even be T cells, since they appear more as mixed leukemia. The patient in this case appears to have a classical T-cell ALL. Most patients with this type generally have a large mediastinal mass, but this patient did not.

T-cell ALL is particularly difficult to treat after relapse and very few, if any, patients survive. The goal is to prevent a relapse. With the pediatric protocols, the relapse rate is low, particularly in younger adults. Unfortunately, all immunotherapies previously discussed, such as blinatumomab, CAR T cells, and inotuzumab, are only active in ALL of the B-cell lineage. They are not effective—and even contraindicated—in patients with T-cell ALL.

Eunice S. Wang, MD Yes, when I speak with other experts about potential immunotherapies or other targeted agents, there seem to be only limited options for the treatment of T-cell ALL.

Dan Douer, MD A novel agent, BMS-906024, is a ϒ-secretase inhibitor that inhibits NOTCH1 activity. Approximately half of the patients with T-cell ALL have an activating NOTCH1 mutation. BMS-906024 is being evaluated in a phase 2 clinical trial in adult

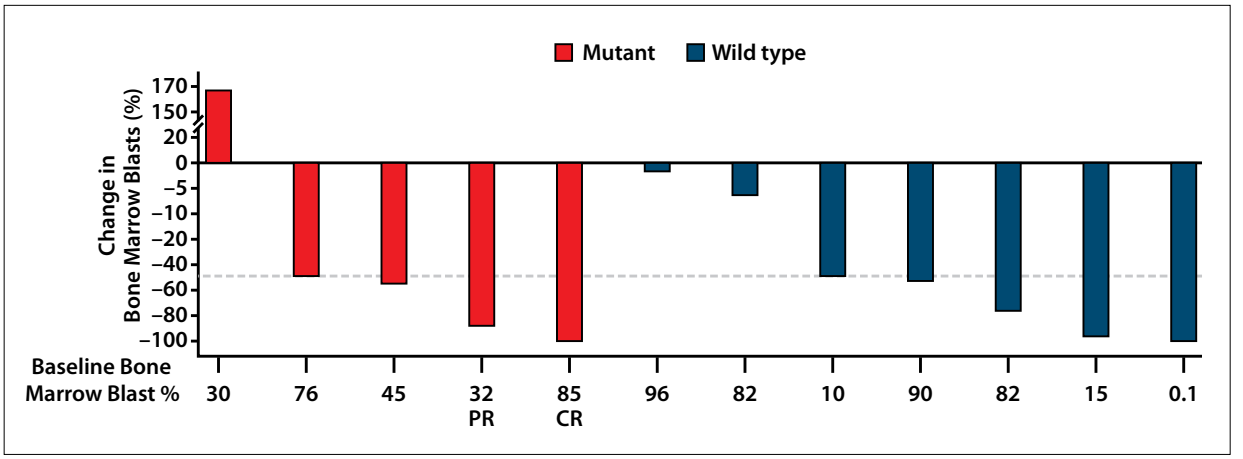

Figure 5. Phase 1 results in a study of BMS-906024, a novel γ-secretase inhibitor. Maximum percent reduction in bone marrow blasts from baseline is shown. Adapted from Zweidler-McKay PA et al. The safety and activity of BMS-906024, a gamma secretase inhibitor (GSI) with anti-notch activity, in patients with relapsed T-cell acute lymphoblastic leukemia (T-ALL): initial results of a phase 1 trial [ASH abstract 968]. *Blood*. 2014;124(suppl 21).[3]

patients with relapsed T-cell ALL.[3] Preliminary results on a total of 25 patients that had received BMS-906024 were presented at the ASH 2014 meeting.[3] A total of 8 patients had at least a 50% reduction in bone marrow blasts, including 1 formal CR and 1 PR (Figure 5). Further, 3 of these 8 patients had 98% to 100% clearance of bone marrow blasts.

We noticed that enrollment into the BMS-906024 trial is limited by the fact that most patients with T-cell ALL have a poor performance status resulting from a large mediastinal mass associated with cardiac problems, as well as pericardial and pleural effusions.

Elias J. Jabbour, MD We have had a similar experience. These patients typically have bulky disease at relapse. It seems that these anti-NOTCH therapies are not very effective at this point in the disease. If they will be shown to be beneficial, it will likely be in patients with minimal disease.

Eunice S. Wang, MD Many of these NOTCH-directed therapies have been in development for several years. Unfortunately, I have not seen any robust responses with these agents. This might be because in the relapse setting, the T-cell ALL is so aggressive that this type of agent cannot significantly impact on disease burden in these patients.

Dan Douer, MD A small percentage (5%) of T-cell ALL cases have the NUP214-ABL1 translocation.[4] These patients can respond to imatinib and other tyrosine kinase inhibitors. It is important to perform a genetic screening in all patients with T-cell ALL, because if this translocation is present, a patient can be managed well with tyrosine kinase inhibitors.

Eunice S. Wang, MD In our center, all of our patients with relapsed/refractory ALL ideally undergo full genomic profiling. As you mentioned, identification of any mutations or overexpressed kinases that can be therapeutically targeted may give us more treatment options.

Dan Douer, MD Yes, we have the same procedure.

Elias J. Jabbour, MD We also do the same. However, we still see a very poor outcome with these patients.

Case Description

A 79-year-old woman with pancytopenia underwent a bone marrow biopsy revealing a new diagnosis of B-cell ALL with normal karyotype. She received frontline therapy with the CALGB 8811 protocol, consisting of a first induction course with cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase. Her treatment was complicated by hypoalbuminemia, which required a dose reduction of L-asparaginase for liver dysfunction. She achieved a CR after just 1 induction cycle. Given her age, it was decided that she should go on to receive further intensification, consolidation, and maintenance therapy, per the CALGB 8811 protocol. After completing a total of 14 courses of maintenance chemotherapy, she remained on observation-only for more than a year.

Unfortunately, on routine follow-up, she was found to have new thrombocytopenia, with a reduction in her platelet count to 75,000 cells/mm^3. A disease restaging bone marrow biopsy performed at that time revealed early evidence of relapse, with the presence of 2.4% malignant

lymphoblasts by flow cytometric analysis. Although FLAG-based chemotherapy was discussed as an option, at this point, the patient was frail and fairly debilitated due to long-standing issues with inoperable lumbar stenosis. She was disheartened about experiencing disease relapse just a year after completing 2 years of intensive chemotherapy. Furthermore, she was hesitant to receive more cytotoxic chemotherapy after the toxicities she had experienced with her frontline regimen. She declined experimental therapies based on a desire to stay an outpatient as long as possible and to avoid the possibility of unknown side effects.

Based on all of these factors, the patient was enrolled on a compassionate exemption protocol to receive vincristine sulfate liposome injection, which at that time was not commercially available. After the third weekly dose, she had improvement in her platelet count and underwent a bone marrow biopsy, which indicated a complete remission. She went on to receive another 2 doses before treatment was stopped at her request, due to the development of progressive neurotoxicity and pain from worsening lumbar stenosis. At this time, her counts had normalized, and there was no evidence of disease on marrow or peripheral blood evaluation.

The patient was admitted to a local rehabilitation center to help her cope with her lumbar stenosis and other back problems. She declined any further treatment or follow-up from the cancer center. After 7 months, just before Christmas, the rehabilitation center contacted the hematologist to report a rising white blood cell count and the reappearance of lymphoblasts on peripheral smear. At this time, the patient agreed to treatment with hydroxyurea to provide some cytoreduction, and to allow her to spend her last holiday with her family. Shortly thereafter, she died in hospice. Her family was extremely grateful that she had been able to live for those extra months, the majority of the time in the outpatient setting.

Case Discussion

Dan Douer, MD This is a great example of a situation in which vincristine sulfate liposome injection is a good choice for palliative care. It is easy to administer, just once weekly through a short infusion, and it can be given in the community setting. The toxicity is mostly limited to neurotoxicity, with no further myelosuppression (any myelosuppression the patient does experience is likely from the disease itself).

Eunice S. Wang, MD The major issues that we have seen with vincristine sulfate liposome injection in our center have been related to constipation, as well as neurotoxicity, the latter of which seems to be cumulative.

Dan Douer, MD At our center, we try to increase the dosage intervals from 10 to 14 days for patients who experience neurotoxicity. There is some experience to support that administering it less frequently does not impact the activity of the agent. Alternatively, the dose could be decreased, but that approach has not been formally studied.

Eunice S. Wang, MD The current prescribing information does not allow for dose reduction. However, if a patient achieves clinical benefit or a CR following weekly doses, it seems reasonable to move to some form of maintenance dosing, which could consist of less frequent drug administration.

Dan Douer, MD True. Even before a CR is achieved, it may be feasible to increase the duration between doses to prevent worsening neurotoxicity. Of course, traditional vincristine is given once per month in frontline maintenance. It is therefore not unreasonable to think that the interval between the administration of vincristine sulfate liposome injection could be extended, given that this formulation delivers more vincristine per dose than the standard agent.

Eunice S. Wang, MD For many patients, their priorities are not prolongation of life but maintenance of a high quality of life and a wish to delay hospital admission for as long as possible. This goal has prompted the use of other strategies, such as the combination of vincristine sulfate liposome injection with corticosteroids, which are both fairly well tolerated, for treatment of patients in the outpatient setting. We have used this approach in the relapsed setting several times, and have seen a slight increase in clinical activity with the combination over single-agent therapy.

Dan Douer, MD The phase 1 trial of vincristine sulfate liposome injection included dexamethasone.[5] However, the phase 2 trial that led to the drug's approval did not include dexamethasone.[6]

Eunice S. Wang, MD We have found that this combination is very well tolerated and beneficial for the treatment of elderly patients with Ph chromosome–negative B-cell ALL, who cannot tolerate a standard induction regimen. I believe that this approach needs to be further investigated.

Dan Douer, MD The theme of our discussion appears to be that when any cell therapy—either stem cell transplant or CAR T cells—is not an option, or has been tried and failed, in the relapse setting, the patient has a very poor prognosis. Having an option like vincristine sulfate liposome injection

combined with corticosteroids may be a good alternative that would allow maintenance (or even improvement) of quality of life and may even offer a slight improvement in survival.

Even in younger patients who fail transplants, many times, the priority is quality of life as their treatment options run out. In these patients, I have found vincristine sulfate liposome injection to be especially useful, because it can maintain quality of life.

Eunice S. Wang, MD You have to realize the limitations of your options for therapy in the relapsed/refractory setting, and what benefits they can truly achieve.

Dan Douer, MD Yes, exactly; you must be realistic.

Eunice S. Wang, MD As the general population ages, we are seeing more and more older individuals being diagnosed with B-cell ALL.

Dan Douer, MD This is likely because the population overall is increasing, and maybe even because more patients are being diagnosed. T-cell ALL is very rare in the elderly. Half of these patients are Ph chromosome–positive. These patients can achieve satisfactory responses with nonaggressive treatments, such as tyrosine kinase inhibitors and corticosteroids. We have a clinical trial that is currently investigating nonchemotherapy approaches to Ph-positive ALL.

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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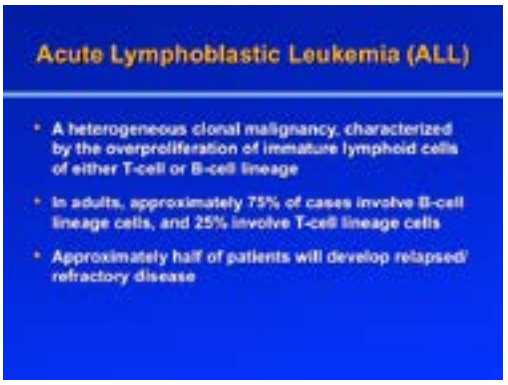

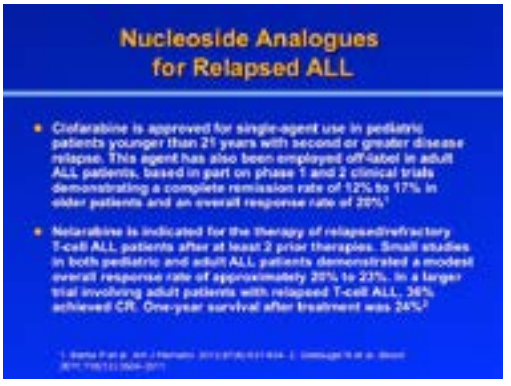

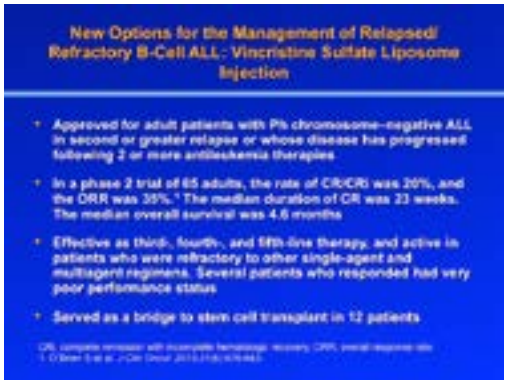

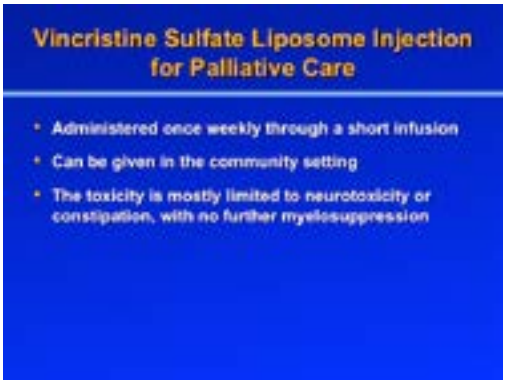

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