Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by the accumulation and proliferation of clonal lymphoid progenitor cells in the bone marrow, periphery, and/or extramedullary sites. The disease is expected to be diagnosed in 6,050 individuals in 2012, with a higher proportion of the diagnoses in children. While ALL is known as a cancer success story in the pediatric setting, with cure rates approaching 90%, the same cannot yet be said of adults. Historically, cure rates for adult ALL are approximately 20% to 40%, depending on patient age and disease characteristics, although these numbers may be improving in younger adults treated with regimens that incorporate targeted therapies. Patients who are at a particularly high risk for a poor outcome include those with rearrangements involving the mixed lineage leukemia (MLL) gene, or with Philadelphia chromosome (Ph)-positive disease. These subtypes occur at a much higher frequency in adults than they do in children. Adults are also far less likely to have favorable cytogenetic features at diagnosis, such as t(12;21) or hyperdiploidy. Unfortunately, most patients will achieve complete remission (CR), and then subsequently suffer a relapse. Salvage regimens for ALL are improving, and targeted therapies are currently being examined in clinical trials. In this review, we will discuss the management of ALL in the adult population, in the context of the recently published guidelines from the National Comprehensive Cancer Network (NCCN). We will focus in particular on the strides being made in salvage and targeted approaches.

FIGURE 1

Outcomes of Frontline HyperCVAD According to Risk Category

Frontline Management

Ph-negative B-ALL

The frontline strategy for the management of adult ALL is similar to that for pediatric ALL: it involves induction chemotherapy, multiple rounds of consolidation, and a prolonged maintenance phase, as well as central nervous system (CNS) prophylaxis. Most protocols call for approximately 3 years of therapy in total. Several regimens are used in the United States; most involve the same key agents, which include vincristine, an anthracycline (eg, doxorubicin or daunorubicin), and a corticosteroid (eg, prednisone or dexamethasone), with or without some form of L-asparaginase. One such regimen is hyperCVAD, in which the combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternates with high-dose methotrexate and cytarabine. Cycles are repeated approximately monthly for a total of 8 cycles; at that point patients move to the maintenance portion of the regimen, which includes daily mercaptopurine, monthly vincristine,
weekly methotrexate, and monthly pulses of prednisone (POMP). Long-term outcomes have been published previously and include a 5-year overall survival (OS) of 38%. Survival was influenced by several prognostic factors that were assessed using multivariable analysis (Figure 1). These outcomes are comparable to those seen with a number of other regimens that are used, depending on center preference. Additional details regarding the hyperCVAD regimen and other NCCN-endorsed regimens for the management of adult ALL can be found in Table 1.

**Chemotherapy Regimens for Adult ALL**

There is an ongoing discussion regarding whether the use of pediatric-inspired ALL regimens may be more effective in adult patients up to 39 years of age. The benefit of using pediatric regimens is thought to derive from more intensive use of corticosteroids, vincristine, asparaginase, and CNS-directed therapy. To date, most of the data on this issue are from large retrospective analyses, which perhaps should not be compared to each other due to the heterogeneity of the patients studied (eg, with regard to age, disease characteristics, etc). Nevertheless, the results of some of these studies have been quite staggering. Stock et al evaluated adolescent patients who were assigned to receive either Children’s Cancer Group (CCG) or Cancer and Leukemia Group B (CALGB) protocol treatment. Patients in both groups achieved CR rates of 90%, but there were substantial differences in both 7-year event-free survival (63% vs 34%; \( P < .001 \)) and OS (67% vs 46%; \( P < .001 \)) favoring the patients on CCG protocols. One important note regarding interpretation of this study is the baseline difference in age between the two groups. There were significantly more 18- to 20-year-old patients in the CALGB cohort. This could potentially explain some of the differences in outcome, considering that 18- to 20-year-olds may inherently do worse than patients between the ages of 15 and 17. Our center is also studying this issue, and patients younger than 40 years currently are prioritized to a single-arm study using the augmented Berlin-Frankfurt-Mnster (BFM) regimen modeled on CCG-1961. The median age of patients enrolled in the current study is 21 years (\( N = 68 \)). The reported remission rate is 96%, with 72% achieving minimal residual disease (MRD) negativity by day 84. There appears to be a distinct difference in outcome between patients who are less than 25 years old and those more than 25 years of age (2-year OS, 88% vs 65%). With short follow-up, overall patient outcomes thus far are comparable to those of a similar group of patients who were treated with the hyperCVAD regimen. Presently, the NCCN guidelines recommend treating patients aged 15 to 39 years with one of several published pediatric-inspired regimens.

L-asparaginase, an enzyme used to deprive lymphoblasts of the nonessential amino acid asparagine, is considered an important component in pediatric ALL regimens. It is also included in several of the commonly used adult regimens, but the cumulative dose is generally less than that of the pediatric programs. A pegylated form of the drug allows for continuous exposure over a period of weeks, reducing the number of infusions or injections a patient would be subjected to if receiving the conventional preparation. Recently, a study from the German Multicenter Study Group for Adult ALL (GMALL) was presented indicating that intensifying the dose of pegylated asparaginase during induction and consolidation improved the survival of younger patients with standard-risk disease at baseline. In this regimen, the drug was well tolerated; however, there was a significant increase in the incidence of grade 3/4 hyperbilirubinemia, which led to treatment interruptions that were found to have a prognostic impact on the outcome. Other potential toxicities that pose a problem include pancreatitis, thrombosis, allergic reaction, hyperglycemia, and hypofibrinogenemia. This makes it highly important to determine the optimal dose and timing of drug administration to prevent or avoid adverse effects that may compromise further antileukemic therapy. If the pegylated formulation is used, these problems can be delayed, such that they typically arise 1 to 2 weeks after a dose is given. A detailed expert review of asparaginase toxicity and its management has recently been published.

Approximately 50% of patients’ leukemic blasts express the CD20 antigen. The prognostic role of CD20 expression in ALL is controversial; nonetheless, targeted therapies directed against this marker have been developed. Recent data from the MD Anderson Cancer Center have indicated that the addition of rituximab (Rituxan), a monoclonal antibody against CD20, to the hyperCVAD regimen improves OS in younger patients. These results were confirmed by a European study that also evaluated the role of monoclonal antibody therapy when added to conventional chemotherapy.
Ofatumumab (Arzerra) is another CD20-targeted monoclonal antibody currently approved for the management of relapsed and refractory chronic lymphocytic leukemia.[19] The binding site of ofatumumab is distinct from that of rituximab, and ofatumumab has been shown to be active in rituximab-refractory settings.[20] Based on the available data, ofatumumab is being evaluated in combination with the hyperCVAD regimen in adults with newly diagnosed ALL.[21]

**T-ALL**

Within the distinct subtype of the disease represented by T-lineage ALL, patients are very heterogeneous. Outcomes are highly variable, dependent on the immunophenotype and molecular characteristics displayed by the leukemic cells.[22] The genetic basis of one subset of poor-risk patients,[23] termed early T-cell precursor ALL, was recently described.[24] The authors noted that, interestingly, the genomic picture was consistent with that of myeloid hematopoietic stem cells, and that therapy directed at this lineage might be expected to improve the response rates and outcome. They also identified mutations commonly found in myeloid malignancy, such as RAS and FLT3 mutations. Other groups have identified FLT3 mutations in 34% of patients with this subtype of T-ALL.[25]

In general, the treatment of T-ALL is similar to that used for B-ALL, and the NCCN guidelines make no specific recommendations regarding the frontline management of the former. Efforts are currently being made to incorporate into the treatment plan drugs that selectively target T cells. Nelarabine (Arranon) is a nucleoside analog that is catabolized to arabinosylguanine triphosphate in vivo. It was developed after it was noted that patients with purine nucleoside phosphorylase (PNP) deficiency suffered a marked T-lymphopenia mediated by the intracellular accumulation of deoxyguanosine triphosphate.[26,27] While nelarabine is approved for relapsed ALL, ongoing studies are attempting to clarify its role in frontline treatment.

**Ph-positive B-ALL**

Ph-positive ALL continues to pose a major challenge in the adult population. Allogeneic stem-cell transplantation (alloSCT) is regarded as the only curative intervention for this subset of patients. Recently, the incorporation of small-molecule tyrosine kinase inhibitors (TKIs) has improved outcomes for these patients. The addition of imatinib (Gleevec) to conventional chemotherapy has been proven superior to chemotherapy alone in several trials that have been published or presented to date.[28] However, in most of these reports, alloSCT still appears to be an important component of consolidation therapy.

Dasatinib (Sprycel) is a second-generation TKI that has enhanced potency against the BCR-ABL protein compared to imatinib, as well as the ability to block the SRC family of kinases.[29] The SRC kinases have been implicated as being required for the development of Ph-positive ALL.[30] Dasatinib also retains activity against most known tyrosine kinase domain mutations that confer resistance to imatinib.[31] Recently, dasatinib was found to be superior to imatinib for the initial treatment of chronic myeloid leukemia (CML) in chronic phase.[32] These favorable characteristics made it appropriate to test combination chemotherapy with the addition of dasatinib in the frontline setting for adult ALL. In a clinical trial with recently published results, 35 patients with newly diagnosed Ph-positive ALL were treated with hyperCVAD + dasatinib.[33] Dasatinib was administered at a dose of 100 mg/d for the first 14 days during the induction and consolidation cycles. If patients completed the consolidation phase, they went on to receive monthly vincristine and prednisone while continuing on dasatinib, 100 mg/d. Ninety-four percent of patients achieved a CR, and the estimated 2-year survival was 64%. A very low percentage of patients proceeded with upfront alloSCT (4 of 36), and it will be important to assess whether dasatinib therapy throws into question the conventional notion that a transplant is absolutely indicated for all patients who are fit and have an adequate stem-cell source. However, additional follow-up is required before that can be determined.

Although the dasatinib data are quite encouraging, patients still relapse, and there are specific kinase domain mutations that are not sensitive to any commercially available TKI. The most notorious mutation for any Ph-positive malignancy is the T315I mutation, which confers resistance to imatinib and dasatinib, as well as to nilotinib (Tasigna). Patients with Ph-positive ALL receiving dasatinib in a European study appeared to develop the T315I mutation at a relatively high frequency, making it important to develop and examine options for combating this problem.[34] One strategy might be to utilize a TKI that has activity against T315I-mutated disease, such as ponatinib. Ponatinib is a rationally designed molecule that has activity against nearly all known BCR-ABL kinase domain mutations.[35] It is currently being evaluated as a frontline strategy in combination with the...
The NCCN guidelines recommend approaches similar to those described above. Available data indicate that it is important to start a TKI as soon as the presence of the Philadelphia chromosome is confirmed. The guidelines do not specify a preference for which TKI to initiate in the frontline setting. Despite the fact that outcomes appear to be improving with current therapies, the NCCN appropriately recommends first and foremost that patients be considered for ongoing clinical trials. Patients at our center are enrolled either on a study evaluating ponatinib plus chemotherapy, or on a cooperative group trial evaluating the previously described regimen of dasatinib plus chemotherapy.

### Bone Marrow Transplantation

AlloSCT is the ultimate form of potential consolidation for patients who achieve CR after induction chemotherapy. There has recently been debate regarding the ideal candidates for alloSCT in first CR. It had been widely accepted that patients with high-risk disease (with varying definitions of high-risk disease, although most included age, white blood cell count at presentation, and presence of the Philadelphia chromosome) should undergo alloSCT in first CR if a suitable donor could be identified (most well studied is the use of a matched sibling). The current NCCN guidelines also endorse such a strategy. However, an analysis of the large Medical Research Council (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) E2993 study revealed that patients with standard-risk disease who had a stem-cell donor had improved OS compared with those who had no donor (5-year OS, 62% vs 52%; \( P = .02 \)). Paradoxically, this study also found that high-risk patients did not benefit when evaluated on a donor-vs-no-donor basis. These results are in disagreement with those of other large studies, possibly because of differing definitions of high-risk disease as well as differences in chemotherapy regimens employed. Most clinicians find it unrealistic that all patients with standard-risk disease be referred for alloSCT, and they prefer a risk-adapted approach that might modify a patient’s risk status over time. Currently, this is largely achieved by monitoring a patient’s MRD status at varying time points during induction and consolidation chemotherapy. Patients who achieve MRD-negative status at protocol-defined points have excellent outcomes with chemotherapy alone. These standard-risk patients can thus be spared transplant-related morbidity and mortality, which can be substantial. Conversely, patients who are MRD-positive will almost universally suffer from relapse, and those who were previously considered standard risk are shifted into the high-risk category. AlloSCT is beneficial for these patients, primarily if they achieve post-transplant MRD-negative status.

Although salvage therapy is discussed below, it is important to note that the ultimate goal of the chemotherapy regimen is to achieve remission so that the patient can move forward to alloSCT. Patients with relapsed disease have a very poor outcome, with a median OS of 24 weeks. In one of the largest series published to date, alloSCT in patients with relapsed disease led to improvement in 5-year OS compared with patients who received chemotherapy alone (16% to 23% vs 4%).

### Salvage Therapy

The general prognosis for adults with relapsed or refractory ALL is poor, with the median OS ranging between 4 and 7 months. As would be expected, patients who are resistant to initial induction therapy, or those who have a CR duration of less than 12 months, do particularly poorly. The expected 5-year OS for adults with relapsed ALL is 5% to 10%, although some groups report improved outcomes for patients with a first CR of greater than 2 years. There are several drugs and regimens for the salvage setting endorsed by the current guidelines, but most of...
these strategies are inadequate, and patients should always be considered for enrollment in a clinical trial first. There are several very promising new agents under investigation, and patients should be referred to centers that are accruing on these protocols.

Conventional strategies

For patients who do not qualify for participation in a clinical trial, the decision regarding salvage strategy is largely based on duration of first remission, performance status, and organ function. It is also very important to consider drug classes and agents that the patient has not yet been exposed to. In addition, one must revisit the cytogenetic and molecular characteristics of the leukemia to devise an appropriate treatment plan.

An augmented version of the hyperCVAD regimen has been developed for use in adults with relapsed ALL.[43] The program includes intensified doses of dexamethasone and vincristine, and the addition of pegylated asparaginase to the traditional hyperCVAD backbone. Ninety patients were enrolled in a trial of this regimen, most of them in first relapse, with 80% having received standard hyperCVAD prior to experiencing recurrent disease. The overall response rate in the study was 64%, with 47% of the patients meeting the definition of CR. The 30-day mortality was less than 10%. This may thus be an ideal regimen for relapsed patients who have not received prior L-asparaginase.

Clofarabine (Clolar) is a nucleoside analog approved for the treatment of pediatric ALL in the third-line setting.[46] Several combination approaches have also been explored in the pediatric and adult patient populations. Recently, a group from France tested two clofarabine-containing regimens in patients with relapsed ALL.[47] The first regimen consisted of clofarabine, dexamethasone, mitoxantrone, etoposide, and pegylated asparaginase. The CR rate was 41%, with an early death rate of 14%. Five of 37 patients experienced grade 3/4 neurologic toxicity. The second regimen tested was a combination of clofarabine and cyclophosphamide. This program also led to a relatively high CR rate of 50%, with very little early mortality and minimal unexpected toxicities. A multicenter phase II trial was also conducted in a group of pediatric patients using clofarabine combined with etoposide and cyclophosphamide.[48] These patients were heavily pretreated, with 84% receiving the regimen as second or higher salvage. The CR rate in this study was 28%, and several patients were able to move on to alloSCT. Patients who had undergone alloSCT prior to being enrolled in this study seemed to be predisposed to severe liver toxicity (eg, veno-occlusive disease [VOD]), and the study was eventually amended to exclude this group. The Programa Espaol de Tratamiento en Hematologia (PETHEMA) group has published their experience with several clofarabine-based regimens in adults.[49] They have reported a CR rate of 31% and manageable toxicity, with several patients being able to proceed to alloSCT. Most of these patients had been treated with two or more chemotherapy regimens.

For patients with T-ALL, nelarabine as a single agent has shown activity in the pediatric and adult settings.[26,50] One of the concerning adverse effects of nelarabine is neurotoxicity, which can manifest peripherally or centrally. For this reason, alternative dosing strategies are being explored to optimize the risk-to-benefit ratio. A study is underway evaluating the safety of giving nelarabine via continuous infusion over 5 days.[51] As mentioned previously, nelarabine would ideally be incorporated into the frontline management of these patients, and studies are ongoing.

On August 9, 2012, the US Food and Drug Administration (FDA) approved the labeling for the use of vincristine sulfate liposomes (Marqibo) in patients with relapsed and/or refractory Ph-negative adult ALL. The drug was studied in relapsed patients who had received at least two previous chemotherapy regimens. It is given as a weekly intravenous infusion at 2.25 mg/m2.
As discussed earlier, using rituximab and ofatumumab as examples, target-directed therapy against antigens expressed on the surface of leukemic cells represents an attractive strategy for fighting this disease and improving patient outcomes. A description of currently available and investigational monoclonal antibodies can be found in Table 2. In addition to CD20, CD19 and CD22 are also antigens that are highly expressed on B lymphoblasts.[52] Monoclonal antibodies against CD19 and CD22 are moving into advanced stages of development, and have demonstrated a high degree of activity, even in the most refractory settings.

**Anti-CD22 antibodies.** The rapid internalization of CD22 upon receptor binding makes it an excellent target for monoclonal antibody-cytotoxic chemotherapy conjugates.[53] Once inside the cell, the toxic component is released, ultimately leading to cell destruction and death. Theoretically, this allows for a minimal dose of chemotherapy to be delivered directly to the leukemic blasts, thus minimizing off-target toxicity.

Inotuzumab ozogamicin is a monoclonal antibody against CD22 that is linked to calicheamicin, a potent cytotoxin that induces double-stranded DNA breaks. The initial clinical trial of this agent was a dose-ranging study conducted in patients with B-cell non-Hodgkin lymphoma.[54] Objective responses were documented in 39% of patients who underwent treatment. The maximum tolerated dose was determined to be 1.8 mg/m² administered every 3 to 4 weeks. Reversible thrombocytopenia was the most frequently encountered toxicity. A phase II study was subsequently conducted in patients with relapsed ALL.[55] An initial dose of 1.3 mg/m² was given to the first three patients to ensure safety, but most patients went on to receive 1.8 mg/m². Patients with CD20-positive disease could have rituximab added to inotuzumab starting on cycle 3 if they exhibited stable disease or no improvement. Forty-nine patients were enrolled, and the majority (73%) received inotuzumab as second or higher salvage. Fourteen percent of patients had previously undergone alloSCT. After a median of 2 cycles of therapy, the overall response rate was 57%, with most patients achieving complete marrow response with incomplete recovery of platelets or peripheral blood cell counts. Fever within 48 hours of drug administration was the most common nonhematologic toxicity, occurring in 59% of patients. Other important toxicities included elevations in bilirubin and hepatic transaminases. Of 49 patients, 22 were treated and subsequently went to alloSCT. Of concern post-transplant was the development of clinical VOD in five patients (23%). Several of these patients had also received thiotepa or clofarabine as part of the preparative regimen, which are known to be potentially hepatotoxic. Two of the four patients undergoing a second alloSCT had clinical evidence of VOD post-transplant. Importantly, alloSCT did not appear to confer a survival benefit, potentially due to the refractoriness of the disease in the patients studied or to transplant-associated complications. Also, the addition of rituximab did not appear to benefit patients who received it according to protocol. MRD was assessed in most patients who responded to treatment, but MRD negativity did not correlate with improved survival.

A weekly schedule of inotuzumab was recently explored in an attempt to optimize the benefit-to-risk ratio based on the pharmacodynamics and pharmacokinetics of the drug.[56] Twenty patients were enrolled, and inotuzumab was given according to the following schedule: 0.8 mg/m² IV on day 1, 0.5 mg/m² IV on day 8, and 0.5 mg/m² IV on day 15. Of note, this is the same cumulative dose per cycle as was given in the every-3-to-4-week schedule. Patients received a median of 2 cycles, with an overall response rate of 50%. The toxicity profile was similar to that of the previous study, with transient elevations of bilirubin and transaminases occurring in 35% of patients. Notably, however, there have been no instances of clinical VOD, including in the four patients who proceeded with alloSCT after receiving inotuzumab.

**Overall Response Rates (ORR) of Inotuzumab vs Conventional Chemotherapy**

These data are encouraging given the refractory nature of the disease in the patients who were treated. The response rates seen with inotuzumab compared to the rates seen with conventional chemotherapy in the salvage setting are presented in Table 3.

**Anti-CD19 antibodies.** CD19 is a surface receptor with nearly universal expression on B-ALL
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accumulate, it will be important to move the most active agents to the frontline management currently being tested in patients with relapsed and refractory disease. As data continue to some of the most promising agents are still in the initial stages of clinical development, and thus are recently been studied is the potential for corticosteroid-induced up-regulation of CD20 expression, the varying degrees of expression of this antigen on lymphoblasts. An interesting concept that has chemotherapy regimen. The use of monoclonal antibodies against CD20 is potentially hampered by the varying degrees of expression of this antigen on lymphoblasts. One arm of blinatumomab is designed to bind CD3-positive cytotoxic T cells, while the other recognizes CD19. Upon binding to CD19, the T cell becomes activated, thereby leading to the death of the malignant cell. Because of its short half-life, blinatumomab is given as a continuous infusion for 4 weeks, followed by a 2-week treatment break. The agent was initially used in adult patients with ALL who had persistent or resurgent MRD after induction or consolidation therapy.[59] This population would be expected to be at very high risk for clinical relapse with continuation of conventional chemotherapy alone. Of 20 patients enrolled, 16 converted to MRD-negative status, and 8 patients subsequently went on to alloSCT. One patient had to be taken off study after the development of a seizure disorder, which was reversible after discontinuation of the blinatumomab. Other common toxicities included fever and lymphopenia. The GMALL group subsequently initiated a study to evaluate blinatumomab in patients with clinically relapsed disease. The results were updated this year at the American Society of Clinical Oncology annual meeting.[60] This is an ongoing phase II trial evaluating multiple dosing strategies in order to minimize toxicity (all regimens have been given as 28-day infusions with 14 days of rest). By the end of 2 cycles of therapy, 68% of patients achieved the study definition of CR or CR with incomplete hematological recovery. The final dose selected was 5 mcg/m2/d for 7 days, followed by 15 mcg/m2/d for 21 days. The most common adverse events included fever, headache, and tremor. Seizures were also noted in this study, as well as other CNS events, such as confusion. Premedication and supportive care strategies are being developed to prevent and manage these issues.

Case presentation. The current status and potential of the above options is best seen through a brief case presentation.

KA is a 30-year-old man who complained of a several-week history of fever, fatigue, and shortness of breath. His white blood cell count at presentation was 265,000/μL. A bone marrow biopsy was performed. The biopsy results and physical findings were consistent with a diagnosis of mixed-phenotype leukemia with B and myeloid features. Cytogenetics include t(4;11)(q21;q23). The immunophenotype analysis revealed a clonal population of cells positive for CD19, CD22, CD33, CD56, CD38, CD15, CD66, and CD184. Because of the mixed phenotype, the patient was induced with a combination of idarubicin, cytarabine, vincristine, and dexamethasone. He achieved CR after one cycle. The patient then received one cycle of consolidation, followed by a matched-related donor alloSCT. Seven months post-transplant, the patient was found to have relapsed disease. The patient was enrolled on a clinical trial using the anti-CD22 antibody inotuzumab ozogamicin. After one cycle, the patient achieved CR, as well as MRD negativity by multiparameter flow cytometry. He went on to receive one additional cycle of inotuzumab, followed by a second matched-related donor alloSCT. Two years after transplant, the patient remains in CR, with no evidence of the t(4;11)(q21;q23) or MRD by flow cytometry. This case describes a dire situation encountered far too often in the clinic. This patient had very high-risk disease at baseline, and was appropriately taken directly to alloSCT after achieving a first CR. Relapsing within 1 year of the transplant normally would place this patient in a situation in which further therapy might be offered for palliation, but in which the possibility of cure, or even of attaining another CR, would be considered bleak.

Future Directions and Perspective

It is clear that the incorporation of monoclonal antibodies is changing the treatment paradigm for adults with ALL. Thus far, the only antibody that has been evaluated as part of the frontline treatment strategy is rituximab, and its benefit was demonstrated when added to an accepted chemotherapy regimen. The use of monoclonal antibodies against CD20 is potentially hampered by the varying degrees of expression of this antigen on lymphoblasts. An interesting concept that has recently been studied is the potential for corticosteroid-induced up-regulation of CD20 expression, which would broaden the applicability of these agents.[61] Some of the most promising agents are still in the initial stages of clinical development, and thus are currently being tested in patients with relapsed and refractory disease. As data continue to accumulate, it will be important to move the most active agents to the frontline management
setting. Inotuzumab ozogamicin is able to induce molecular remission in a large number of patients, which is critical to outcomes for patients undergoing induction and consolidation chemotherapy. Monoclonal antibodies also appear to be less toxic than conventional cytotoxic agents, making them particularly interesting for elderly patients with ALL. A strategy utilizing inotuzumab in combination with reduced doses of cyclophosphamide, vincristine, and corticosteroids (alternating with methotrexate and cytarabine) in elderly patients is being studied in an ongoing trial.[62] The anthracycline is omitted completely from this protocol, as it tends to cause significant problems for this age group. A far-reaching goal is to one day incorporate multiple monoclonal antibodies into the frontline approach, thereby minimizing the use of cytotoxic chemotherapy. The challenge will be to determine the optimal way to sequence such combinations, and the amount of cumulative exposure necessary to maintain durable responses (ie, cure). Monoclonal antibodies are large molecules, so it will be important to monitor the impact increased use has on isolated CNS disease. The prophylactic approach may also have to be modified. Targeted approaches for T-ALL need to be improved. Monoclonal antibodies active in this subtype are lacking, and this should be a focus of drug development going forward. Gamma-secretase inhibitors that block NOTCH receptor signaling are exciting biologically, but experience in the clinic has been far less promising.[63]

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