# Management of Acute Lymphoblastic Leukemia in Older Adults

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**Abstract:** Acute lymphoblastic leukemia, commonly known to affect the younger population, is a disease that is affecting the elderly in an increasing amount as the human life span continues to lengthen. Traditional cytotoxic agents are intolerable to elderly individuals owing to comorbidities, weakened immune systems, and organ dysfunction. Alternative agents and regimens are needed to allow for elderly patient to tolerate full cycles of therapy while providing complete and durable remissions. With the advent of targeted agents, such as monoclonal antibodies and bispecific T-cell engagers, a number of options have proven themselves to be effective in the elderly and optimal for tolerability. Here, we review and discuss the literature addressing regimens that use new agents, such as blinatumomab, inotuzumab ozogamicin, and venetoclax, and those that use modified dosing strategies of traditional chemotherapy.

Keywords
Acute lymphoblastic leukemia (ALL), elderly patients, older adults

## Introduction

The age distribution of acute lymphoblastic leukemia (ALL) is bimodal, with high incidences seen in children and older adults. Specifically, nearly 20% of patients with ALL are older than 55 years. ALL is a result of a proliferation of lymphoid progenitor cells in the bone marrow and tissue, which leads to an immunosuppressed state. Without treatment, ALL causes death within weeks or sometimes days after the appearance of symptoms.[1] Even with treatment, complete remission (CR) is difficult to achieve in elderly patients, and remissions tend to be short-lived. As the general population grows and individual life expectancy increases, it is expected that by 2030, elderly individuals will account for 20% of the population.[2,3] The importance of expanding the number of therapies that provide deep, long-lasting remissions in elderly patients, while weighing efficacy against the risk for toxicity, will continue to be paramount as the years go on.

## The History of Outcomes in the Elderly

For decades, cytotoxic chemotherapy has been the backbone of treatment in B-cell ALL. The mechanism by which these agents work is true to their definition—they obliterate cancer cells. Unfortunately,

collateral damage also occurs and results in multiple issues, such as prolonged immunosuppression, organ toxicity, exacerbation of chronic diseases (eg, diabetes, hypertension and other cardiovascular diseases, chronic kidney disease), poor nutrition, and inadequate self-care. All of these decrease the ability of patients to withstand formal treatment with chemotherapy.[4] The damage is magnified in elderly patients, resulting in a higher death rate and a decrease in 5-year overall survival (OS) of approximately 20%.[5,6]

Additional complications arise in the elderly population beyond the risks that come with age and comorbidities. In comparison with their younger counterparts, older patients are at higher risk for disease with poor prognostic features.[7,8] From a cytogenetic standpoint, these include complex karyotype and low hypodiploidy/near-triploidy. Additionally, the risk for Philadelphia chromosome (Ph)–positive disease is approximately 50% in patients older than 50 years, whereas it is 20% among patients with ALL overall.[9,10] The Ph-like subtype, characterized by high-risk genetic abnormalities, is seen in 24% of elderly patients and includes a variety of rearrangements in the *ABL* class genes, *CRLF2* genes, and—less commonly—the *JAK/STAT* genes.[5] In regard to molecular risks, the incidences of *TP53* and *IKZF1* are higher in elderly patients as well.[11-14]

In 2021, Sasaki and colleagues published a real-world analysis of patients with ALL, various treatment options, and the outcomes of treatment.[15] By comparing outcomes based on data recorded decades prior with the outcomes seen in today's studies, the researchers were able to grasp an understanding of the evolution of care for patients with ALL. They found that survival rates from 1980 through 2017 were 22% in persons aged 60 to 69 years and 7% in those aged 70 years and older. We have seen an uptick in these numbers in more recent years with the advent of targeted therapy, including oral agents, bispecific T-cell engagers, and antibody-drug conjugates. Most recently, the survival rates have been 29% in persons aged 60 to 69 years and 13% in those aged 70 years and older.

As we continue to acquire a better understanding of the molecular makeup of this disease, we can isolate differences not only among disease states but also among subsets of patients within disease states, thereby maximizing the outcomes achieved with a variety of therapies. As previously mentioned, elderly individuals are predisposed to having disease with several high-risk cytogenetic and molecular features. With an understanding of this issue, along with the composition of ALL, we have been able to develop and evaluate tailored therapies and agents that reduce the collateral damage that elderly patients cannot withstand. We discuss the evolution of these agents, including bispecific monoclonal antibodies, antibody-drug conjugates, reduced-dose chemotherapy, targeted tyrosine kinase inhibitors (TKIs), and B-cell lymphoma 2 (BCL2) inhibitors.

## Antibody-Drug Conjugates and Bispecific Monoclonal Antibody–Based Options

Monoclonal antibodies have taken the cancer world by storm, most importantly dominating the treatment algorithms for elderly patients with ALL.[16] The 2 most noteworthy agents in this group are blinatumomab (Blincyto, Amgen), a bispecific T-cell engager (BiTE), and inotuzumab ozogamicin (Besponsa, Pfizer), a conjugated monoclonal antibody. Both agents have been approved for use in the United States for the treatment of B-cell ALL, making them an excellent option for elderly patients.

Blinatumomab functions by simultaneously engaging the CD19 attachment on B cells and the CD3 attachment on T cells, inducing a T cell–mediated attack on the corresponding leukemia B cells. Blinatumomab is administered as a continuous infusion that is given for 28 days every 42 days.[17] Formerly, bag changes were required every 2 days, but now the bags can be changed every 7 days because of improved pharmaceutical compounding practices. This change makes blinatumomab a logistically viable option in the outpatient setting. Unlike standard cytotoxic chemotherapy agents, blinatumomab is not expected to cause myelosuppression, although some cases of thrombocytopenia have been seen.[18] A unique side effect of blinatumomab is neurotoxicity, which most commonly manifests as tremors or confusion. Cytokine release syndrome may also occur. These adverse events can be prevented or mitigated by escalating the dose slowly after initiation to ensure tolerability, and by administering corticosteroids preemptively. Most side effects are easily alleviated by simply pausing the infusion because blinatumomab is a continuous infusion with a very short half-life. Corticosteroid treatment can also be used. Overall, blinatumomab functions well logistically and without significant toxicity.

Blinatumomab was studied in older patients with B-cell ALL as part of the phase 2 Southwest Oncology Group (SWOG) 1318 study.[18] Participants older than 65 years were treated with a standard dose of blinatumomab for up to 2 cycles. If CR was achieved, then 3 more cycles of blinatumomab were administered. Blinatumomab treatment was followed by 18 months of the maintenance therapy standard in this population: prednisone, vincristine, oral methotrexate, and 6-mercaptopurine (POMP). The ages of the 29 patients eligible for enrollment ranged from 66 to 84 years; 55% of them had standard-risk disease, and 34% had high-risk disease. The OS rate at 6 months was 79%, and the overall response rate

**Table 1.** HyperCVAD vs MiniCVD Dosing

| | Cyclophosphamide | Doxorubicin | Vincristine | Dexamethasone | Cytarabine | Methotrexate[a] |
|---|---|---|---|---|---|---|
| **HyperCVAD** | 300 mg/m$^2$ | 50 mg/m$^2$ | 2 mg | 40 mg | 2 g/m$^2$ | 200/800 mg/m$^2$ |
| **MiniCVD** | 150 mg/m$^2$ | None | 2 mg | 20 mg | 0.5 mg/m$^2$ | 50/200 mg/m$^2$ |

[a]The first dose is administered over 2 hours, followed by the second dose over 22 hours, for a total 24-hour infusion.

(ORR) after the first cycle was 66%. Additional studies have been conducted that corroborated these findings, furthering the success and usage of blinatumomab in elderly patients.[19]

Inotuzumab consists of a monoclonal antibody conjugated to a cytotoxic agent known as calicheamicin. Inotuzumab attaches to the CD22 portion of a leukemia B cell, which internalizes the calicheamicin, resulting in DNA destruction and apoptosis of the cell. Because the effects of calicheamicin are slightly longer than those of blinatumomab, inotuzumab is given in split doses once weekly for a cycle of 21 or 28 days.[20] Unlike blinatumomab, inotuzumab at full doses has been found to have myelosuppressive properties, mainly owing to the addition of calicheamicin to the monoclonal agent. Additionally, low incidences of veno-occlusive disease (VOD) and other forms of hepatic injury have been associated with its use. At MD Anderson Cancer Center, it is common practice to use ursodiol as a preventative agent for this toxicity. It is also suggested that inotuzumab not be administered within 3 months prior to patients undergoing stem cell transplant or receiving fludarabine, to avoid compounding the risk for toxicity.

A phase 2 study was conducted in patients older than 55 years with newly diagnosed Ph-negative ALL.[21] The patients, whose median age was 64 years, received split weekly doses of inotuzumab totaling 1.8 mg/m$^2$, along with intrathecal chemotherapy. During subsequent cycles, the doses were slightly reduced to a total of 1.5 mg/m$^2$. A complete or incomplete remission was achieved in all patients after the first cycle, with a 1-year OS rate of 82.4%. Patients were assessed for minimal residual disease (MRD), and 74% tested negative. As previously mentioned, the incidence of myelosuppression was high (leukopenia, 64%; anemia, 54%; thrombocytopenia, 68%), and 31% of the patients had elevated liver enzymes. All these values trended down during subsequent cycles, implying increased tolerability at the slightly lower dose.

## Reduced-Intensity Chemotherapy

It is well established that the backbone of ALL treatment is cytotoxic chemotherapy consisting of high doses of cytarabine, methotrexate, vincristine, cyclophosphamide, doxorubicin, and a corticosteroid (dexamethasone or prednisone), a commonly used regimen known as hyperCVAD. It is also well understood that cytotoxic therapy causes prolonged myelosuppression, especially in elderly and pretreated patients.[22] In recent years, the concept of administering these same drugs at lower doses has been studied in various patient populations, notably the elderly. It is hoped that with these reductions, the risk for myelosuppression and corresponding infection will be mitigated, expanding the population of patients eligible for the benefits of treatment with these drugs.

As seen in Table 1, the combination of lower-dose hyperCVAD, also known as miniCVD, omits the anthracycline and halves the doses of the remaining medications with the exception of vincristine, whose dose remains the same.[23] In a phase 2 study conducted at MD Anderson Cancer Center, miniCVD was given in combination with reduced-dose inotuzumab (a total of 1.0-1.3 mg/m$^2$ per cycle) for 4 cycles, followed by blinatumomab consolidation therapy (dosing detailed in Table 2), then 2 years of POMP and blinatumomab maintenance.[24,25] At the initiation of this protocol, the treatment design included 8 cycles of hyperCVAD followed by 3 years of maintenance. However, after the new findings of benefit with inotuzumab and blinatumomab, the protocol was amended to include 4 cycles of miniCVD with doses of inotuzumab, followed by 4 cycles of blinatumomab. The maintenance phase was altered to include 12 cycles of POMP and 1 cycle of blinatumomab with every 3 cycles of POMP. Like Dr Emil Freireich, who initiated the concept of combination chemotherapy, Kantarjian and colleagues hoped to achieve more durable remissions by targeting disease on multiple levels with a combination of new and old agents. Additionally, it was hoped that decreasing the amount of cytotoxic therapy and replacing it with less toxic monoclonal antibodies would enable older patients to tolerate therapy in its entirety

This study enrolled 70 patients, whose median age was 68 years. Baseline risk descriptors included *TP53* mutations in 41% of patients and adverse cytogenetics in 27% of patients. The response rate was 98%, with 88% of the patients achieving full CR and 96% having undetectable MRD by flow cytometry. The mortality at 1 month was zero, with a slight bump to 3% mortality after the second month. After a follow-up period of 4 years, 78% of patients remained in CR, with an OS rate of 50%. The

**Table 2.** MiniCVD, Blinatumomab, and Inotuzumab Combination Schema in Patients Younger Than 70 Years

| | CVD | Ara-C/MTX | Blinatumomab | Inotuzumab | POMP |
|---|---|---|---|---|---|
| **Cycle 1** | Yes | - | - | Yes: 0.9 mg/m$^2$ | - |
| **Cycle 2** | - | Yes | - | Yes: 0.6 mg/m$^2$ | - |
| **Cycle 3** | Yes | - | - | Yes: 0.6 mg/m$^2$ | - |
| **Cycle 4** | - | Yes | - | Yes: 0.6 mg/m$^2$ | - |
| **Cycles 5-8** | - | - | Yes | - | - |
| **Cycles 9-11**[a] | - | - | - | - | Yes |
| **Cycle 12**[a] | - | - | Yes | - | - |

[a]Cycles 9 through 12 should be repeated 3 more times, for a total of 4 maintenance cycles.

Ara-C/MTX, cytarabine and methotrexate; CVD, cyclophosphamide, vincristine, and dexamethasone; POMP, prednisone, vincristine, oral methotrexate, and 6-mercaptopurine.

rate of death was highest (45%) in individuals older than 70 years, which translated to a 4-year OS rate of 34% for that age group. The rate of death in CR was also higher in patients older than 70 years than in those aged 60 to 69 years, at 50% vs 22%, respectively. Causes of death in CR included sepsis, which occurred only in patients older than 70 years, as well as secondary myelodysplastic syndrome and acute myeloid leukemia (AML), which in 3 of the 4 cases occurred in patients older than 70 years. VOD, gunshot wounds, dementia, and end-stage renal disease were among the other causes of death. Because of the increased mortality noted in individuals older than 70 years, the study was amended to decrease the number of miniCVD and inotuzumab combination cycles from 4 to 2, thereby reducing the dose of inotuzumab to 1.5 mg/m$^2$ total for both cycles. Consolidation was changed to start at cycle 3 with 4 cycles of blinatumomab, all completed along with a total of 8 sessions of intrathecal chemotherapy. As discussed earlier, a few of the expected adverse events occurred. VOD developed in 6 patients, one of whom was treated shortly after transplant, with no difference between the numbers of patients who did and did not receive blinatumomab.

To make best use of the data, a propensity score analysis was conducted to compare outcomes in the study patients vs those of patients who received high-intensity chemotherapy with standard doses of hyperCVAD.[26] The comparison was essential to understanding the magnitude of benefit elderly patients derived from the reduced-dose option. Response rates were higher with the miniCVD backbone than with the hyperCVAD backbone, at 98% vs 88%, respectively, and early death rates were lower, at 0% vs 8%, respectively. The death rate was also lower with miniCVD than with hyperCVAD among those in CR, at 5% vs 17%, respectively. The 3-year OS rate was nearly doubled with miniCVD vs hyperCVAD, at 63% vs 34%, respectively.

This study continues to accrue patients, and the protocols have been extrapolated to treatment outside clinical trials, including at MD Anderson Cancer Center. Promising outcomes continue to be seen in our elderly patients. The study additionally has been expanded to use this treatment in the setting of relapse in younger, more fit patients, with continued benefit. Although the combination uses multiple agents, it is exactly this multimodal attack on cancer that has brought leukemia therapy to the forefront in inducing longer and deeper remissions.

## BCL2 Inhibitors

Rapidly expanding its functionality, the BCL2 inhibitor venetoclax (Venclexta, AbbVie) has been showing benefit in all types of hematologic malignancies, with new studies opening to assess its utilization in solid tumors as well.[27,28] Commercially available for chronic lymphocytic leukemia (CLL) and AML, especially in unfit elderly patients, venetoclax is working its way into the lymphoblastic world as well.[29,30] As an inhibitor of the anti-apoptotic BCL2 protein, it works to ensure the lysis of cells with BCL2 overexpression, which is present in both B and T cells. Hence, its most expected adverse event is tumor lysis syndrome. As with blinatumomab, the use of dose escalation has helped to mitigate venetoclax-associated adverse events. Currently in CLL, it is standard practice to ramp up doses on a weekly basis over 4 weeks. In AML, a more rapid ramp-up is commonly used in patients with elevated white blood cell counts, with the dose increased each day. Over the years, the expression of BCL2 in lymphoblastic cells in preclinical data has become better understood, particularly in patients with *KTM2A* rearrangements, thereby validating the use of BCL2 inhibitors for treatment.[31-33]

Venetoclax was initially studied in younger, heavily pretreated patients with ALL. In a phase 1 study, 47

patients with B-cell or T-cell ALL (median age, 27 years) and a median of 4 prior lines of therapy were treated with venetoclax and the investigational multi-BCL inhibitor navitoclax in combination with chemotherapy. The ORR was 60%, the MRD negativity rate was 58%, and the median OS was 7.8 months.[34] With the use of multiple BCL-targeted agents, pro-survival pathways can be blunted. Apoptosis mechanisms are then promoted, specifically through increased mitochondrial membrane penetration and caspase activation. This finding paved the way for Jain and colleagues to use a similar combination regimen in elderly patients, both treated and untreated.[35] When a maximum dose of 400 or 600 mg of venetoclax (cohort-dependent allotment) was used in combination with miniCVD therapy, an ORR of 100% and a CR rate of 90% were seen in untreated individuals. In patients with relapse, a CR rate of 37.5% and an MRD negativity rate of 25% were seen. As expected, febrile neutropenia was the most frequent grade 3 toxicity, secondary to the myelosuppression seen with this regimen. These positive outcomes and advancements in therapy help to provide a platform for future combinations of BCL2 inhibitor therapy in patients with ALL. Larger studies continue to be conducted both in B-cell and T-cell ALL to confirm the initial findings of benefit.

## Philadelphia Chromosome–Positive Disease

Ph-positive disease in ALL has been associated with decreased survival; however, the advent of TKI therapy targeting BCR-ABL has begun to mitigate this negative outcome. The incidence of Ph-positive disease increases with age, so that the management of this abnormality is vital to improving outcomes in elderly patients. In young and fit individuals, the standard of care is to use a regimen such as hyperCVAD in combination with one of the targeted TKIs, such as dasatinib (Sprycel, Bristol Myers Squibb) or ponatinib (Iclusig, Ariad). Each TKI within this family has its own set of expected adverse events. Dasatinib is best known for its risk for pleural effusions, whereas ponatinib is best known for its risk for cardiovascular-associated events, such as hypertension.[36] However, only ponatinib can overcome the T315I mutation, which is most responsible for resistance in this disease and often difficult to circumvent.

Because monotherapy with agents such as blinatumomab has been successful in elderly patients, combination of a monoclonal antibody with a TKI seems only appropriate in this population. In the phase 2 GIMEMA study, dasatinib was used in combination with blinatumomab in 63 patients with a median age of 54 years (the oldest patient was 82 years old).[37] A total of 98% of these patients achieved a CR following induction, with 60% achieving a molecular response after the second cycle. Another multicenter study, this one conducted retrospectively, looked at the outcomes of 26 patients treated with a combination of blinatumomab and ponatinib.[38] A total of 96% of patients experienced a complete morphologic remission, and 89% had a complete molecular response.

In the most recent study done at MD Anderson Cancer Center, Short and colleagues treated 28 patients (median age, 59 years) with a combination of blinatumomab, ponatinib, and 12 doses of prophylactic intrathecal chemotherapy.[39] The median age of patients in the cohort with newly diagnosed disease was 62 years, so this combination was a viable option in elderly patients. The study revealed an ORR of 100% in the cohort with newly diagnosed disease and an OS rate of 94% in the entire study population. There were no treatment-related deaths at follow-up, and no patients in the cohort with newly diagnosed disease underwent allogeneic stem cell transplant.

The use of combinations of chemotherapy-based regimens in elderly patients continues to expand, with numerous continuing and new studies. As part of the European Working Group on Adult ALL (EWALL), Rousselot and colleagues conducted a study of reduced-dose chemotherapy in combination with continuous dasatinib in elderly individuals.[40] The induction therapy consisted of dexamethasone, vincristine, and intrathecal chemotherapy. Induction was followed by consolidation with 2 different alternating regimens, the first comprising intermediate-dose methotrexate and asparaginase and the second consisting of intermediate-dose cytarabine. Consolidation was followed by maintenance therapy for 2½ years with vincristine and dexamethasone. A total of 71 patients with a median age of 69 years were treated, in whom the CR rate was 96%. At 5-year follow-up, the OS rate was 45% when deaths due to non–leukemia-related causes were excluded. Of the 36 patients who finally relapsed, 75% were shown to have a T315I mutation, untreatable with dasatinib therapy. A 3-log reduction of *BCR-ABL1* transcripts was achieved in 65% of patients during consolidation.

Additional studies are always warranted to pursue durable and permanent remissions in elderly patients with Ph-positive disease. Currently, the use of miniCVD and blinatumomab in combination with a TKI continues to be studied at MD Anderson Cancer Center in elderly patients, in the hope of providing an additional treatment option (NCT03589326). However, it should be noted that excellent options are currently available, as previously discussed—specifically, the combination of blinatumomab with a TKI, which provides durable remissions in this patient population and has a safe and tolerable toxicity profile.

**Table 3.** Summary of Treatment Regimens and Outcomes

| Trial | Disease | Agents | N | Median Age, y (range) | CR/ CRi, % | Early Mortality/Death in CR, % | OS, % |
|---|---|---|---|---|---|---|---|
| *Historical Regimens* | | | | | | | |
| **O'Brien (2008)**[22] | Ph-negative B-cell ALL, frontline | *Induction*: CYC; VCN; dexamethasone alternating with MTX; Ara-C<br>*Maintenance*: POMP | 122 | NR (>65) | 84 | -/34 | 20, 5 y |
| **Sive (2012)**[43]<br>*Review article* | Ph-negative B-cell ALL | MRC/ECOG, CALGB, hyperCVAD, SWOG 819, GIMEMA 0288, PETHEMA ALL 96, SWOG 9400, EWALL | 100 | 56 (55-65) | 73 | 18/23 | 21, 5 y |
| **Assi (2017)**[44] | Ph-positive B-cell ALL | Blinatumomab 9 µg/d, days 1-7<br>Blinatumomab 28 µg/d, days 8-28<br>TKI: ponatinib, dasatinib, or bosutinib | 12 | 65 (30-77) | 84 | -/- | 73, 12 mo |
| **Rousselot (2016)**[40] | Ph-positive B-cell ALL | *Induction*: VCN + dexamethasone<br>*Consolidation*: MTX, asparaginase, or Ara-C<br>*Maintenance*: VCN + dexamethasone<br>*Intrathecal*: MTX, Ara-C, and MP<br>*TKI*: dasatinib 100-140 mg/d | 71 | 69 (59-83) | 96 | -/- | 45, 5 y |
| **Gökbuget (2012)**[45] | Ph-negative B-cell ALL/T-cell ALL, frontline | ***Berlin-Frankfurt-Münster–based regimen***<br>*Induction*: daunorubicin, VCN, prednisone, PEG-asparaginase<br>*Consolidation*: CYC, Ara-C, 6-MP, VCN, PEG-asparaginase, doxorubicin, dexamethasone<br>*Maintenance*: POMP<br>*Intrathecal*: Ara-C and MTX | 268 | 67 (55-85) | 76 | 14/6 | 23, 5 y |
| *Modern Regimens* | | | | | | | |
| **Kantarjian (2018), Short (2019)**[23,25] | Ph-negative B-cell ALL, frontline | *Induction*: miniCVD; CYC; VCN; dexamethasone alternating with MTX; Ara-C<br>*Inotuzumab*: given cycles 2-4<br>*Maintenance*: POMP<br>*Intrathecal*: Ara-C and MTX | 70 | 68 (60-81) | 88 | 0/32 | 50%, 4-y |
| **Advani (2018)**[18] | Ph-negative B-cell ALL, frontline | Blinatumomab 9 µg/d, days 1-7<br>Blinatumomab 28 µg/d, days 8-28<br>Followed by POMP for 18 mo | 29 | 75 (66-84) | 66 | 0/- | 65%, 1-y |
| **Stelljes (2020)**[21] | Ph-negative B-cell ALL, frontline | *Cycle 1*: inotuzumab 0.8 mg/m$^2$ on day 1 and 0.5 mg/m$^2$ on days 8 and 15; dexamethasone 10 mg/m$^2$ on days 7-8, 14-17<br>*Cycles 2-3*: inotuzumab 0.5 mg/m$^2$ on days 1, 8, and 15<br>Intrathecal: MTX, Ara-C, and dexamethasone | 29 | 64 (56-80) | 100 | -/7 | 82%, 1-y |
| **Short (2021)**[39] | Ph-positive B-cell ALL, frontline | Blinatumomab 9 µg/d, days 1-7<br>Blinatumomab 28 µg/d, days 8-28<br>Ponatinib 30-45 mg/d | 28 | 59 (25-83) | 100 | -/<br>- | 94%, 1-y |

ALL, acute lymphoblastic leukemia; Ara-C, cytarabine; CALGB, Cancer and Leukemia Group B; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CYC, cyclophosphamide; d, day; ECOG, Eastern Cooperative Oncology Group; EWALL, Scientific Working Group on Adult Acute Lymphoblastic Leukemia; GIMEMA, Gruppo Italiano Mallatie Ematologiche dell'Adulto; hyperCVAD, high-dose cytarabine, methotrexate, vincristine, cyclophosphamide, doxorubicin, and dexamethasone or prednisone; mo, month(s); miniCVD, vincristine with low-dose cyclophosphamide and dexamethasone; MRC, Medical Research Council; MP, methylprednisolone; MTX, methotrexate; 6-MP, mercaptopurine; NR, not reported; OS, overall survival; PETHEMA, Programa de Estudio y Tratamiento de las Hemopatias Malignas; Ph, Philadelphia chromosome; POMP, prednisone, vincristine, methotrexate, and 6-mercaptopurine; SWOG, Southwest Oncology Group; TKI, tyrosine kinase inhibitor; VCN, vincristine; y, year(s).

## Conclusion

Currently, numerous studies of treatments for ALL are available, many of them emphasizing the treatment of elderly patients. Some of interest include a study of AMG404, a programmed death 1 (PD-1) protein inhibitor in combination with blinatumomab (NCT04524455), and a study of natural killer cell therapy, based on the concept behind chimeric antigen receptor (CAR) T-cell therapy (NCT02727803). Most recently, brexucabtagene autoleucel (Tecartus, Kite Pharma), an autologous anti-CD19 CAR T-cell therapy, was approved for the treatment of adult patients with ALL, with potential benefit in elderly patients who are fit.[41] Additionally, randomized studies comparing the use of blinatumomab vs conventional chemotherapy are underway in the pediatric population, paving the way for similar studies in elderly patients.[42]

Our key take-home concept is to ensure that a treatment option is first effective and then—equally important—tolerable. Tolerability is key in elderly patients, in whom comorbidities and tenuous health status are to be anticipated. The advent of monoclonal antibodies over the past few years has created an entirely new realm of treatments that are more targeted than standard chemotherapy, so that the deleterious effects of DNA-damaging agents on healthy cells can be avoided.

The therapy options for elderly patients with ALL continue to grow; Table 3 provides a summary of the studies discussed. A comparison of concepts and death rates from a decade ago with those of today makes it evident that the current outcomes can be claimed to be miraculous. Our goal is to continue to extend the life span of patients with a disease that was formerly inevitably fatal by further improving our understanding of ALL. With new combinations of established therapies, we can continue to diversify treatment options and achieve more durable remissions.

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