This review will discuss the pathophysiology associated with the del(17p13.1) interphase cytogenetic abnormality, the current generally poor outcomes in affected patients, currently approved therapeutic agents, and new agents now undergoing investigation.

**Introduction**

Chronic lymphocytic leukemia (CLL) is a very heterogeneous disease with significant variation in clinical presentation, time to disease progression, survival, and aggressiveness of clinical course. Multiple ongoing laboratory-based studies are attempting to better understand the pathophysiology of this disorder, identify risk factors that portend poor survival, and provide targets for future therapeutic agents. A subgroup of patients who have repeatedly been identified as having a poor response to therapy are those with del(17p13.1) on interphase cytogenetics. Although there has been much progress in CLL therapeutics over the past few years, progress in this patient subgroup has continued to lag behind that seen in other populations. This review will discuss the pathophysiology associated with the del(17p13.1) interphase cytogenetic abnormality, the current generally poor outcomes in affected patients, currently approved therapeutic agents, and new agents now undergoing investigation.

**Pathophysiology**

The chemotherapy resistance observed in del(17p13.1) patients is likely related to malfunction of the tumor suppressor protein p53. In humans, the gene that regulates this protein (TP53) is located on the short arm of chromosome 17 (17p13.1).[1] Patients with deletion of 17p have a homozygous TP53 gene, which becomes inactivated by mutation in the vast majority of these patients,[2-4] leading to total lack of function of the p53 pathway (Figure 1). To date, studies have indicated that ~80% of patients with del(17p13.1) also have TP53 gene mutations, and only 4% to 18% of patients studied have TP53 mutations but do not have del(17p13.1).[2,4] However, the region deleted is large, and loss of other genes in this area or associated genomic instability could also be a driver of poor outcomes in these individuals. In response to cellular DNA damage caused by radiation or therapeutics, a normal cell responds by up-regulating the level of p53 protein. [5] Cell-cycle arrest is then induced by p21WAF1 (wild-type p53-activated fragment) through inactivation of
cyclin-dependent kinase 2 (CDK2), which blocks the transition of the cell cycle from the G1 phase to
the S phase.[6,7] Then cellular and DNA repair enzymes can repair DNA lesions before DNA
replication, preventing perpetuation of potentially harmful mutations.[5,8] However, if DNA damage
is extensive and irreparable, p53 induces apoptosis of the cell, a process mediated by BAX (BCL-2
[B-cell lymphoma 2]-associated protein X) and down-regulated by BCL-2, and the damaged cell is
eliminated.[7,9] The function of p53 is therefore paramount to cellular response to cytotoxic
chemotherapies—yet p53 is defective in CLL patients with del(17p13.1) or TP53 mutations.

Epidemiology

With the advent of interphase fluorescence in situ hybridization (FISH) and its heightened diagnostic
sensitivity, the del(17p13.1) aberration was detected in ~7% of a large group of mostly untreated
patients.[10] Rates of detection of del(17p13.1) following fludarabine therapy have been reported as
being as high as 30%,[11] indicating clonal evolution of the disease to withstand chemotherapy.
Because the abnormal p53 clones are resistant to chemotherapy, they initiate a negative selection
process that slowly increases the number of cells that carry these abnormalities, causing subsequent
adverse clinical repercussions.[12] These patients have consistently demonstrated poor survival and
a shorter interval from diagnosis to therapy.[7,10,13] The landmark study using interphase FISH for
cytogenetic classification of CLL predicted that patients with del(17p13.1) typically require therapy
within 1 year of diagnosis and have a meager median overall survival (OS) of only 32 months.[10]
Additionally, the landmark trial that established fludarabine, cyclophosphamide, and rituximab
(Rituxan) (FCR) as standard-of-care front-line therapy for CLL patients resulted in improved
progression-free survival (PFS) and OS when the patients were evaluated all together, but
demonstrated that expression of del(17p13.1) was the strongest negative predictive factor for these
variables. For the del(17p13.1) patient group, the rate of complete response (CR) was only 5%,
3-year PFS was 18%, and 3-year OS was 38%—compared with rates of 44%, 65%, and 87%,
respectively, for the group as a whole.[13] The del(17p13.1) group did not benefit from the addition
of rituximab.

In contrast to the majority of historical data, a recent study by Tam et al reviewed 99
treatment-naive (TN) CLL patients with del(17p13.1) and discovered that there is significant clinical
heterogeneity within this group. The researchers cautioned against making therapeutic choices
solely on the basis of the presence of this cytogenetic abnormality.[14] In the published results of
this study, several attempts were made to document this heterogeneity, including by means of short
follow-up. Also, patients with del(17p13.1) who also had unmutated IGVH and Rai stage (Rai) ≥ 1
demonstrated worse survival.[14] Another study indicated that a loss of TP53 of ≥ 10% conferred a
markedly inferior prognosis, compared with the prognosis in patients with < 10% loss of TP53.[15]
Rossi et al used quantitative reverse-transcription polymerase chain reaction (qRT-PCR) to evaluate
a series of patients with and without del(17p13.1) cytogenetics.[16] This study identified a microRNA
(miR) fingerprint typically expressed in del(17p13.1) patients. It also identified higher levels of
miR-21 and low levels of miR-181 in these patients.[16] Many other ongoing research studies
attempt to risk-stratify patients within this high-risk group, with the goals of better understanding
disease pathology and discovering new and effective therapeutic targets.

Treatment Overview

TABLE

Summary of Results for CLL Patients With Del (17p13.1) in Clinical Trials
As described above and documented in a large number of previous trials, current available treatments have demonstrated discouraging efficacy in the high-risk group of patients who express del(17p13.1). In addition, the small overall number of patients in this group has thwarted progress in the improvement of therapy, with most clinical trials including a very limited number of patients with this cytogenetic feature (Table). In this section of the article, we describe the current guidelines for therapy. In subsequent sections, we describe prior trials and promising agents currently under investigation.

In general, the clinical spectrum of CLL at initial presentation is very heterogeneous. Therefore, a patient usually needs to meet specific criteria prior to initiation of therapy, since some patients can be observed for years without change in clinical condition. Some investigators have proposed that CLL patients who have del(17p13.1) may require earlier therapy because of their known poor prognosis. However, recent trials (described in detail above)[14-16] have suggested heterogeneity even within this group, with some early-stage patients demonstrating a reasonable treatment-free survival. Thus, the indications for therapy in a patient with del(17p13.1) remain the same as for a CLL patient without this deletion. Indications for consideration of treatment that have been established by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)[17] include the presence of any one of the following:

- Clinical symptoms (fevers, night sweats, weight loss, or painful lymphadenopathy or splenomegaly).
- Cytopenias (hemoglobin < 11 g/dL or platelets < 100 × 10^12/L) without other causes.
- Autoimmune hemolytic anemia or thrombocytopenia (idiopathic thrombocytopenia purpura [ITP]) poorly responsive to standard therapy.
- Rapidly progressive disease (lymphocyte count rising to > 300 × 10^9/L, or rapidly enlarging lymph nodes, spleen, and liver).

Isolated mild thrombocytopenia (platelets 70–100 × 10^12/L) can often represent chronic ITP and can be followed closely if no other symptoms are present. A bone marrow biopsy can sometimes help determine whether disease or a combination of disease and ITP is driving this isolated thrombocytopenia.

Once the necessity of treatment has been established, most clinicians turn to the National Comprehensive Cancer Network (NCCN) guidelines for recommendations regarding choice of therapy. Straightforwardly, the NCCN guidelines indicate that there is no set standard-of-care for patients with del(17p13.1) cytogenetics; if eligible, these patients should be enrolled in a clinical trial. Per these guidelines, if a patient achieves a CR or a partial response and is a candidate for transplant, allogeneic stem-cell transplant (alloSCT) should be considered. However, the currency of the NCCN guidelines is limited by the amount of time and strict regulations required to update these recommendations. Research in the field of CLL is constantly bringing new therapeutic options to the fore, and guidelines can become outdated quickly. That being said, the NCCN guidelines are updated as expeditiously as possible based on new published data and represent the most comprehensive and up-to-date source for treatment suggestions. Below, the therapeutic options for patients who are ineligible for a clinical trial will be discussed—for the front-line setting, for the relapsed/refractory (RR) setting, and for the elderly patient population. Figures 2 and 3 depict the treatment algorithms used for patients with del(17p13.1) in the front-line and RR settings, respectively, at our institution.

**Treatment of Younger Patients**

**Chemoimmunotherapy**

**FIGURE 2**

Treatment Algorithm for Patients at Initial Diagnosis of Del(17p13.1) Chronic Lymphocytic Leukemia

**FIGURE 3**
As described in the section on epidemiology, above, standard therapy with FCR is not ideal for this group. However, the CLL-8 trial did demonstrate that del(17p13.1) patients who received front-line FCR (n = 21) had a trend towards an improved overall response rate (ORR) (71% vs 46%, \( P = .08 \)) and improved 3-year PFS (17.9% vs 0%, \( P = .052 \)), compared with patients who received fludarabine and cyclophosphamide without rituximab (n = 16), demonstrating a borderline benefit of rituximab in therapy for these patients.[13] Although the ORR trended towards improvement in this group, the 3-year PFS of only 17.9% indicates that the response to FCR is not durable. FCR can therefore be viewed as a cytoreductive therapy for del(17p13.1) patients that is best followed by consolidation with alloSCT or an alternative investigational therapy. In the relapsed setting, the outcomes with FCR in this population are poor. A large study showed a CR of 0% and an ORR of 35%, with a short median PFS (5 months) and median OS (10.5 months) in this population (n = 20),[18] leading to a recommendation against this regimen in relapsed del(17p13.1) patients. Additional studies have been completed with a fludarabine-and-rituximab-only regimen; however, there are insufficient data available to recommend this regimen in the del(17p13.1) group.

When rituximab and bendamustine (Treanda) were combined for therapy of front-line or relapsed CLL, the outcomes in the del(17p13.1) subset were bleak, with a 43% partial response in the front-line patients (n = 3 of 7)[19] and only one patient (7%) responding, and a median PFS of 6.8 months and median OS of 16.3 months in the relapsed population (n = 14).[20] This regimen should not be recommended in this subgroup.

Oxaliplatin (Eloxatin) and cytarabine have been added to fludarabine and rituximab (OFAR) in an attempt to improve outcomes in the setting of relapsed CLL. A trial using this regimen demonstrated an ORR of 33% in fludarabine-refractory CLL patients. The RR del(17p13.1) patients in this trial (n = 15) also demonstrated an ORR of 33%; however, no further subgroup analysis was completed. For the group as a whole, median response duration was 10 months. The main toxicities were hematologic, with a subset of patients not completing therapy due to these adverse effects.[21]

**Rituximab and high-dose corticosteroids.** Because the addition of rituximab to chemotherapy improved clinical response, and because previous studies had shown response in the relapsed setting to single-agent high-dose methylprednisolone (HDMP),[22] Bowen et al combined rituximab and HDMP for the treatment of relapsed CLL and found an ORR of 56% in patients with del(17p13.1) (n = 9).[23] Subsequently, Castro et al used this regimen in a front-line clinical trial (n = 36); they achieved an ORR of 96% and a median PFS of 30.3 months, with good tolerance of the regimen.[24] Only one patient had del(17p13.1) in this trial, but the HDMP regimen can be used for patients with limited options, who cannot tolerate more aggressive regimens. Patients on this regimen must receive aggressive prophylaxis against opportunistic pathogens, and even with these preventive measures, mortality due to infectious causes is high. Additionally, the metabolic and psychological complications of this regimen can be severe in some patients. Morbidity and mortality are generally more severe in the refractory group of patients receiving this regimen.

**Alemtuzumab monotherapy.** In light of the success of rituximab, another monoclonal antibody (mAb), alemtuzumab (Campath), which targets CD52, has been extensively studied in this high-risk population—and has shown success. The efficacy of alemtuzumab was initially noted when it was used as a single agent in fludarabine-refractory patients with TP53 mutations and deletions.[25] Following their initial case report, Lozanski et al noted in a larger series of patients a 40% response rate and 8-month median duration of survival in this group,[26] results that were confirmed by several other studies.[11,27] The CAM307 trial, which compared alemtuzumab to chlorambucil, is the only study that provides information on the efficacy of alemtuzumab. The small cohort of patients with del(17p13.1) who received alemtuzumab (n = 11) tended to have a superior ORR (64% vs 20%, \( P = .08 \)) compared with the ORR in the patients who received chlorambucil (n = 10).

However, there was no improvement in PFS, with a disappointing median PFS of 10.7 months in the alemtuzumab group (vs 2.2 months in the chlorambucil group, \( P = .41 \)); moreover, the patients in the alemtuzumab group experienced more neutopenia and cytomegalovirus reactivation.[28] Another notable limitation of this agent, first recognized in the early studies, was that patients with...
bulky lymph nodes (> 5 cm) were less likely to respond to the antibody.[29]

**Alemtuzumab and high-dose corticosteroids.** Using the same rationale as was used in the studies with rituximab and HDMP, and building on the fact that HDMP was previously effective in bulky disease, alemtuzumab was combined with HDMP in a pilot study[30] that led to the multicenter recently published CLL-206 trial. The results of this trial describe the outcomes of both previously untreated (n = 17) and treated (n = 22) CLL patients with del(17p13.1). The regimen showed efficacy—more so in the untreated group—with ORR, CR rate, median PFS, and median OS of 88%, 65%, 18.3 months, and 38.9 months, respectively. (In the previously treated group, these results were 17%, 14%, 6.5 months, and 19.5 months, respectively.) The regimen was fairly toxic, especially in patients over the age of 60, with significant grade 3/4 hematologic and glucocorticoid toxicity (67%) and grade 3/4 infection (51%; 68% in patients over age 60). A 5% treatment-related mortality rate was reported.[31] Similarly, the ongoing CLL-20 trial has combined alemtuzumab with oral dexamethasone (with plans for subsequent maintenance alemtuzumab vs alloSCT) for untreated del(17p13.1), relapsed del(17p13.1), and fludarabine-refractory patients. Preliminary reports have demonstrated ORRs of 100% and 78% and CRs of 23% and 0% in the untreated (n = 31) and relapsed (n = 17) del(17p13.1) patients, respectively. Infection and hematologic toxicity have again been concerns with this regimen.[32]

Multiple additional regimens have been attempts to combine alemtuzumab with various chemoimmunotherapeutic agents (eg, the combination of alemtuzumab with FCR[33, 34]); however, insignificant improvements in response and survival with increased risks of severe infectious toxicity do not allow for recommendation of these therapies in the front-line or relapsed setting.

**Ofatumumab.** Ofatumumab (Arzerra) is a human mAb to CD20; it is similar to rituximab but binds at a different epitope and causes more potent complement-dependent cytotoxicity than rituximab. Ofatumumab was recently approved in the relapsed population based on a landmark trial in which it was used as a single agent in fludarabine-refractory CLL patients with bulky adenopathy (> 5 cm) (n = 79) and without (n = 59); the resulting ORRs were 47% and 58%, respectively. The del(17p13.1) patients in the group with bulky adenopathy (n = 14) and without (n = 17) had ORRs of 14% and 41%, respectively. No further subgroup analysis was completed; however, PFS for the entire group was slightly less than 6 months. This regimen was very well tolerated, with primarily grade 1 and grade 2 adverse events reported.[35]

**Reduced-intensity alloSCT**

If a patient is young and otherwise fit and achieves a response with early chemoimmunotherapy regimens, both the NCCN guidelines and the European Group for Blood and Marrow Transplantation consider the presence of del(17p13.1) cytogenetics to be an indication for reduced-intensity alloSCT.[36] A more detailed review on transplantation in this patient group has recently been published.[37] The CLL-3X study indicated that the del(17p13.1) patients (n = 13) who underwent alloSCT demonstrated equivalent outcomes to other cytogenetic groups. The researchers noted a 3-year event-free survival (EFS) of 45% in patients with del(17p13.1), which was consistent with previous studies. Patients with del(17p13.1) who were refractory to chemotherapy at the time of transplant had a significantly shorter EFS (hazard ratio = 2.77; 95% confidence interval = 1.50–5.09).[38] A retrospective study demonstrated a 3-year PFS of 37% for this group (n = 44) and indicated that patients with del(17p13.1) who had had more than three prior therapies had a significantly shorter PFS than those who had received fewer than three prior therapies (19% vs 53%, P = .03).[39]

Although the results of these trials appear promising, it is not clear that the risks of toxicity and transplant-related mortality are balanced by the benefits of prolonged PFS. A prospective trial (Cancer and Leukemia Group B [CALGB] 100701) has been initiated to evaluate this question in previously untreated but symptomatic del(17p13.1) patients. While these trials support the use of transplantation in a young and minimally pretreated population, they cannot be generalized to the typical elderly patient with multiple comorbidities that make pursuit of this modality difficult. All patients with del(17p13.1) who are medically appropriate for reduced-intensity alloSCT should be seen and evaluated by a transplant team early in the course of the disease. For our group, we generally refer such patients at the time we initiate first-line treatment.

**Treatment of Elderly Patients**

The elderly (> 65 years) subgroup of patients with del(17p13.1) cytogenetics pose a particularly challenging treatment dilemma. Although the median age at diagnosis of CLL is 72 years and ~70%
of newly diagnosed patients are older than 65 years,[40] this group has been widely underrepresented in clinical trials, and many of these patients have major medical comorbidities or poor performance status. If an elderly patient has a good performance status, he or she should be enrolled in a clinical trial. If no trial is available, the regimens of alemtuzumab (if no bulky lymph nodes are present) or HDMP + alemtuzumab or HDMP + rituximab could be considered in this group. However, few data exist for alemtuzumab either as monotherapy or in combination with HDMP in the elderly population. A small study (n = 28) using HDMP and rituximab, which included 8 patients over age 70 using this regimen as frontline CLL therapy, demonstrated an ORR of 100% and a CR of 38% in this elderly population; toxicities were minimal. Cytogenetic status was not reported, however.[41] Given the paucity of data in this patient group, clinical studies are needed to better define acceptable and tolerable treatment options. Elderly unfit patients should be referred for palliative care, since there are no therapies for which the benefits outweigh the risks of toxicity.

**New Agents**

As detailed in this review, standard therapies have had consistently disappointing outcomes in the population of CLL patients with abnormalities of del(17p13.1) or TP53 mutations. The future of this subgroup depends heavily on the development of innovative therapies that act with a p53-independent mechanism. There are several promising therapies currently in clinical trials.

**Lenalidomide**

Lenalidomide (Revlimid) is an immunomodulatory drug that may work in part by stimulating the host's own immune system via an increase in the activity of T cells and natural killer cells, which directly induces apoptosis in tumor cells.[42] Additionally, lenalidomide activates CLL cells, making them more recognizable to the immune system; it also increases CD154 expression, thereby activating pro-apoptotic pathways (eg, p73) that can bypass p53.[43] A number of other mechanisms have also been proposed that have recently been reviewed.[44] Eighty RR CLL patients, including patients with high-risk cytogenetic features and bulky lymph nodes, were treated in two phase II studies that demonstrated clinical efficacy. PR was achieved in 29% of the del(17p13.1) patients (n = 14).[45] One of these studies used a higher dose (25 mg/d) for 21 days of a 28-day cycle, but 3 patients experienced severe tumor lysis syndrome (TLS) and 58% had a tumor flare reaction (TFR) (8% had grade 3/4 reactions).[46] The other study used a continuous lower dose (10 mg/d), which resulted in no TLS and TFR in 30%.[47] A subsequent phase I study tested starting at a low dose (2.5 mg/d), with titration up to 20 mg/d to minimize TLS and TFR. In this study, 11.5% (n = 6) achieved PR, and 55.7% (n = 30) achieved stable disease (SD), with a median PFS of ~24 months.[48] Due to lenalidomide’s success, there are ongoing trials evaluating its efficacy as front-line single-agent therapy and in combination with chemoimmunotherapy. One of these studies treated CLL patients over age 65 with lenalidomide and demonstrated clinical efficacy (ORR = 65%, 2-year PFS = 60%) and tolerability in this subset of patients.[49] The six patients with del(17p13.1) did not respond; however, the total number of patients in the study was quite small. Notable efficacy and tolerability have been shown with the combination of lenalidomide and rituximab, both in the front-line[50] and relapsed settings. In the relapsed setting, the ORR of del(17p13.1) patients (n = 15) was 53%, with 13% (n = 2) achieving CR.[51] Registration studies are ongoing with lenalidomide to establish the use of this agent with or without rituximab as one alternative therapy for relapsed del(17p13.1) CLL patients.

**B-cell receptor (BCR) antagonists**

**FIGURE 4**

B-Cell Receptor Stimulation
Ibrutinib (formerly PCI-32765) and GS-1101 (formerly CAL-101) are two of the most successful of these new therapies; they have been especially effective in refractory/relapsed CLL (recently reviewed by Woyach et al[52]). These drugs work by targeting the BCR signaling pathway (Figure 4), which has been found to be aberrantly activated in CLL and to promote CLL cell survival and proliferation.[52] Ibrutinib is an oral, irreversible inhibitor of Bruton’s tyrosine kinase (BTK); it promotes apoptosis and inhibits proliferation, migration, and adhesion in CLL cells.[53,54] A phase Ib/II trial evaluated single-agent ibrutinib in RR CLL patients (n = 61) and TN CLL patients (n = 31), all over age 65; the study participants included 24 patients with del(17p13.1) (RR = 22, TN = 2). At the recommended phase I dose (420 mg/d), the ORR was 67% and 73% in the RR and TN groups, respectively, and estimated 12-month PFS was 88% and 93.3%, respectively. An additional 22% of the RR group achieved a nodal response, with residual lymphocytosis. The initial lymphocytosis was likely due to CLL cell mobilization from the bone marrow, and most patients returned to baseline with a break in treatment or longer-term continuation of the drug. The ORR was independent of high-risk factors, including del(17p13.1). The majority of toxicities were less than grade 2, making this a very tolerable as well as an efficacious regimen.[55] Multiple ongoing studies are investigating ibrutinib in combination with various immunochemotherapy regimens, such as bendamustine and rituximab or ofatumumab.

GS-1101 is an isomeric-selective inhibitor of phosphatidylinositol 3-kinase (PI3K) δ; it inhibits PI3K signaling and induces apoptosis of CLL cells in vitro.[56] A phase I trial using GS-1101 in relapsed CLL patients (n = 54) demonstrated that 84% achieved a ≥ 50% decrease in lymph node and spleen size. However, a > 50% increase in lymphocytosis (temporary in some—similar to the reaction seen with ibrutinib) was seen in 58%, and this resolved in only a subset of patients, thereby lowering the ORR by the IWCLL criteria.[17] The response rate seen in this study was independent of typical high-risk CLL features, notably the presence of del(17p13.1) (n = 19) and bulky adenopathy (n = 44). Median PFS had not been reached at the time of presentation but was > 11 months. Notably, del(17p13.1) patients had a shorter PFS in this study than did other groups. The compound was well tolerated, with limited toxicity reported.[57] Multiple combinations involving GS-1101 are currently in phase II trials, including combinations with rituximab, ofatumumab, and bendamustine and rituximab. Multiple other agents that target the BCR signaling pathway are currently under investigation in clinical trials in lymphoid malignancy, including fostamatinib, dasatinib (Sprycel), AVL-292, GDC-0941, and XL147.

CDK inhibitors

Another promising group of agents that have shown efficacy in the del(17p13.1) population are the CDK inhibitors, most notably flavopiridol and dinaciclib. CDKs are a family of proteins that control most of the steps in the cell cycle and also other functions, such as transcription (among the proteins in this family are CDK7, CDK8, and CDK9). The mechanism by which CDK inhibitors promote cell death in nonproliferating CLL cells has long been an enigma, although recent evidence with flavopiridol suggests endoplasmic reticulum stress is a major mechanism of action.[58] Clinical trials have indicated clinical efficacy for flavopiridol in the RR CLL population. A review of the major phase I[59] and phase II trials[60] involving flavopiridol noted that ORR and PFS were not significantly different between cytogenetic groups, with a 48% ORR and an estimated PFS of 10.1 months in the del(17p13.1) population.[61] Combinations of this drug with chemoimmunotherapy agents have been studied in the phase I setting, with successful results.[62,63] Dinaciclib is a small-molecule inhibitor of multiple CDKs that has been studied in a phase I trial in RR CLL. This trial demonstrated an ORR of 53% in patients with del(17p13.1) (n = 17).[64] Although the CDK inhibitors are efficacious, both flavopiridol and dinaciclib demonstrated increased risk of TLS in their early trials. However, this toxicity has been minimized by alteration of the dosing regimens and aggressive inpatient supportive care during the first two doses of the drug, when the tumor burden is at its highest. Neither of these drugs are currently commercially available.

BCL-2 antagonists

Another novel group of agents are the BCL-2 antagonists navitoclax (ABT-263) and ABT-199. Navitoclax binds to BCL-2, BCL-xL, and BCL-w, thereby halting suppression of BAX and BAK and allowing these proteins to oligomerize and trigger apoptosis of the tumor cells (see Figure 1). In a phase I trial in RR CLL, navitoclax has shown promise by reducing lymphocytosis by more than 50% in 19 of 21 patients (with baseline lymphocytosis). In patients treated with doses ≥ 110 mg/d (n = 26), 35% achieved PR and 33% maintained SD for > 6 months. Similar responses were shown in high-risk groups, including PR in 3 of 9 patients with del(17p13.1), with PFS not yet reached at time.
of publication. The major limiting side effect in this trial was dose-dependent thrombocytopenia, thought to be related to inhibition of BCL-xL. Based on these promising data with navitoclax, another BCL-2 inhibitor, ABT-199, is currently under investigation in phase I trials. ABT-199 is an agent with more specific inhibition of BCL-2; it is hoped that it will be able to limit the thrombocytopenia toxicity while maintaining the clinical efficacy seen with navitoclax.

Conclusion

In summary, the population of CLL patients with del(17p13.1) or other defects in the p53 pathway has consistently demonstrated a poor response to therapy. The p53 defect impairs the CLL cell’s ability to respond to DNA damage inflicted by cytotoxic chemotherapy. Although progress has been made since the clinical significance of this abnormality was discovered, the currently available regimens are substandard, with poor response or unacceptable toxicity. Exciting new agents, which are designed to function in the absence of a functional p53 pathway, are showing much promise, as demonstrated in early clinical trial results. New therapies are clearly needed for the high-risk population of patients with del(17p13.1). Until such therapies are available, we would emphasize the importance of referring these individuals for clinical trials.

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