favorable cytogenetic group had the expected longer survival when given chemotherapy + GO rather than chemotherapy alone. The Southwest Oncology Group has also failed to notice an effect of CD33 SNPs on outcome in adults (*M Othus, 2018, personal communication*).

Even the minority of patients who benefit from GO might benefit more from development of improved anti-CD33 therapeutics.[17] One possibility here is use of bispecific antibodies (BiAbs) that engage CD33 but also direct T cells toward AML cells. An obvious model for this approach is blinatumomab,[18] a CD3/CD19 molecule built in the Bispecific T-cell Engager (BiTE) format. A first series of CD33/CD3 BiAbs, including the BiTE AMG 330 and the tandem diabody AMV-564, have recently entered clinical tests.

Like GO, all CD33 BiAbs (and other CD33-directed therapeutics) currently under investigation recognize the V set domain, which is located distally on CD33. However, preliminary studies with artificial CD33 molecules show that membrane proximal binding enhances the immune effector cell functions of CD33 antibodies (*R Walter, 2018, personal communication*). Development of antibodies recognizing such proximal sites is likely to be an area of examination in GO's second and, hopefully, subsequent acts.

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Lenalidomide can be safely combined with chlorambucil and rituximab in older patients with chronic lymphocytic leukemia

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The clinical activity of lenalidomide in chronic lymphocytic leukemia (CLL) was first reported more than 10 years ago.[1,2] Since then, this agent has been studied in various combinations with anti-CD20 monoclonal antibodies, chemotherapy, chemo-immunotherapy and B-cell receptor (BCR)-targeting agents. These studies have shown clinical responses; however, most importantly, they have also highlighted unique and unexpected toxicities, in particular when lenalidomide was combined with chemo-immunotherapy and targeted agents.

In this issue of *Haematologica*, Kater and colleagues report the experience of the HOVON CLL study group on the feasibility and efficacy of the combination of lenalidomide, chlorambucil, and rituximab in treatment-naïve patients

with CLL.[3] The patients enrolled in this trial were considered ineligible to receive the combination of fludarabine, cyclophosphamide, and rituximab (FCR) because of their older age or the presence of comorbidities. For the first six cycles (induction-I), lenalidomide was given in combination with chlorambucil and rituximab at a starting dose of 2.5 mg, with escalation to 10 mg. The authors report that they were able to administer a median lenalidomide dose of 86.7% of the full dose, with the full dose given to more than 50% of patients. For the next six cycles (induction-II), lenalidomide was given as monotherapy at a dose of 10 mg daily. The median administered dose was 99.7% of the full dose, and the full dose was given to 69% of patients during cycle 6. The results of this phase 1-2 study showed that the combination of lenolidamide, chlorambucil, and rituximab can be safely administered to patients with CLL: grade 3-4 toxicities were mainly hematologic (grade 3-4 neutropenia occurred in 73% and 64% of patients during induction-I and induction-II, respectively), tumor lysis syndrome did not occur, tumor flare reaction occurred in five (9%) patients (mainly grade 2), and two (4%) patients had a thromboembolic event despite thromboembolic prophylaxis. Of 53 patients in induction-I, eight discontinued treatment because of excessive toxicity, whereas five of 42 patients discontinued treatment during induction-II. The authors also report on the activity of this combination:

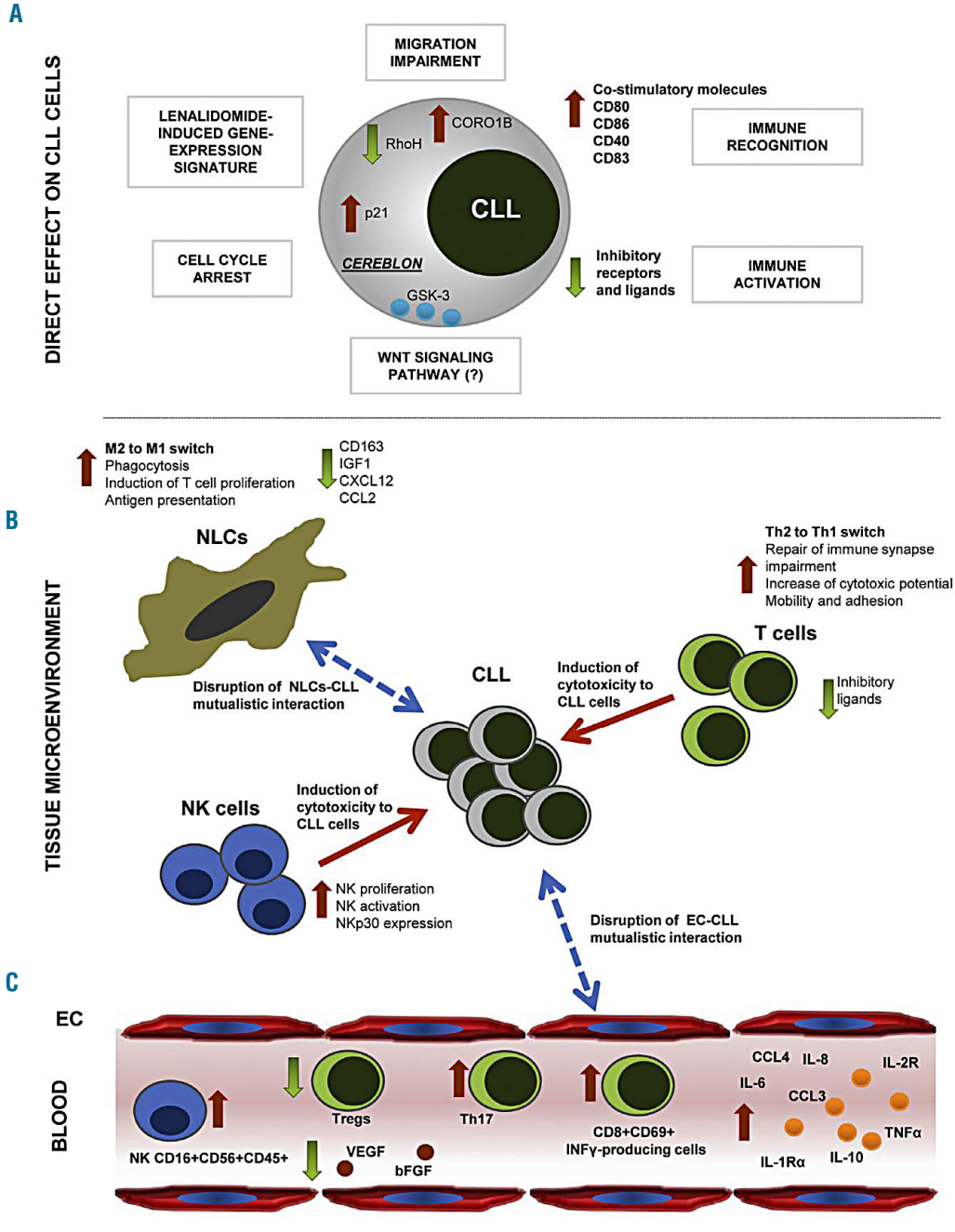

Figure 1. Mechanisms of action of lenalidomide. The mechanisms of action of lenalidomide include: (A) direct effects on CLL cells and (B, C) modification of tumor-microenvironment interactions. This figure is reproduced with permission from Mattei R *et al.*, Lenalidomide in chronic lymphocytic leukemia: the present and future in the era of tyrosine kinase inhibitors. Crit Rev Oncol Hematol. 206;97:291-302. NLCs: nurse-like cells; EC: endothelial cells.

responses were seen in 83% of the patients treated, the median progression-free survival was 49 months, and the 3-year overall survival rate was 95%.

Early monotherapy trials showed that lenalidomide is associated with a unique toxicity profile in patients with CLL, causing tumor lysis syndrome, tumor flare reaction, myelosuppression, and, in particular, neutropenia, skin rash, and diarrhea.[1,2] Particularly severe events, including deaths, were reported in trials with no dose escalation[4] or rapid dose escalation,[5] and tumor lysis syndrome occurred in patients with bulky lymphadenopathy despite proper prophylaxis.[1] After these early experiences, trials with lenalidomide employed stepwise dose escalation strategies with low starting doses (usually 2.5 mg/day), as in the study presented by Kater *et al.*, and managed tumor flare reactions with non-steroidal anti-inflammatory drugs and corticosteroids. Moreover, careful patient selection is recommended. The population included in the study by Kater *et al.* mainly consisted of older but fit patients: 98% were 65 years or older, 87% had a Cumulative Illness Rating Scale score of 6 or lower, and all had a glomerular filtration rate of 60 mL/min or higher at the time of entry into the study.

In the last decade, several lenalidomide-containing combination regimens have been evaluated in patients with treatment-naïve CLL. When lenalidomide was combined with rituximab in the frontline setting, the treatment was generally well tolerated, with the most common grade 3-4 toxicities being neutropenia, anemia, infections, increased transaminase levels, and skin rash.[6,7] However, when different partners, such as chemotherapy agents or targeted drugs, were tested in combination with lenalidomide, some trials documented excessive toxicities that led to early termination of the studies. For instance, a phase 1 study investigating the combination of lenalidomide with fludarabine and rituximab was closed early because of unpredictable reactions and unexpectedly persistent myelosuppression, even when very low doses of fludarabine and lenalidomide were given, which made treatment delivery difficult.[8] Instead, induction treatment with low-dose lenalidomide together with reduced-dose FCR was demonstrated to be safe.[9] In the relapse setting, lenalidomide was evaluated in association with rituximab and ibrutinib; the study investigating this approach showed a high incidence of persistent severe neutropenia that occurred despite growth factor support.[10] This unfavorable toxicity profile, together with poor preliminary efficacy data, discouraged further evaluation of this combination. The combination of lenalidomide with rituximab and idelalisib also showed unacceptable liver toxicity in patients with relapsed or refractory indolent lymphoma.[11]

Regarding efficacy, the single-arm design of the study by Kater *et al.* does not allow a direct comparison of the triple combination with chlorambucil and rituximab. Acknowledging the limitations of cross-trial comparisons, however, the efficacy of the proposed regimen compares positively with that of chlorambucil plus anti-CD20 monoclonal antibodies. In a study conducted by Strati *et al.*,[7] the combination of lenalidomide plus rituximab produced an overall response rate of 73% in treatment-naïve patients, with a complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate of 35%, a median time to treatment failure of 22 months, and a 4-year overall survival rate of 90%. The same treatment combination was explored in a multicenter study, which showed an overall response rate of 88%, of which 15% were CR/CRi, and a median progression-free survival of 19 months.[6]

It is essential to put the data presented by Kater and colleagues into perspective by considering recent changes in the treatment landscape of CLL brought about by the availability of new targeted drugs, such as BTK inhibitors, PI3K inhibitors, and Bcl-2 antagonists, which have also been studied in older patients. In a recent update of the phase III RESONATE-2 trial of ibrutinib, which enrolled patients aged 65 years and older with previously untreated CLL and without del(17p), researchers reported that at a median follow-up time of 29 months, the overall response rate was 92%, the median duration of progression-free survival had not been reached, and the 24-month progression-free survival rate was 89%.[12] Patients carrying abnormalities on chromosome 17 represent a subset of CLL patients with a particularly poor prognosis. In the cohort presented by Kater *et al.*, eight (17%) patients had del(17p), and their progression-free survival rate was lower than that of patients without del(17p) (38% *versus* 59% at 3 years). Notably, in a phase II study that evaluated ibrutinib in a cohort of treatment-naïve CLL patients with TP53 aberrations, the estimated 5-year progression-free survival rate was 74.4%.[13]

That being said, a credit that pertains exclusively to lenalidomide is the role this drug has had in elucidating tumor-microenvironment interactions in CLL. Phenotypic and functional immune defects are known to be associated with CLL; these defects confer an increased risk of infections and autoimmune phenomena and foster leukemia cell proliferation and survival. Several studies have shown that treatment with lenalidomide modulates the cross-talk between tumor cells and various components of the tumor microenvironment. Examples of these effects include the ability to normalize $CD3^+$ T-cell and T_{reg} numbers *in vivo*[14,15] and to restore immunological synapse formation.[16] The antitumoral activities of lenalidomide also appear to be attributable to a direct effect on neoplastic cells; lenalidomide not only enhances immune recognition, but also induces CRBN-mediated upregulation of p21 *in vitro*[17] (Figure 1).

The recent progresses in immunotherapy approaches that exploit the ability to engineer the T-cell receptor, such as chimeric antigen receptor (CAR) T-cell therapy, may revitalize interest in the use of immunomodulatory agents, including lenalidomide, in CLL. Immune dysfunctions are thought to be responsible for the lower efficacy of these approaches in CLL than in other lymphoproliferative diseases. Apheresis products from CLL patients and the derived CAR T-cell products exhibit an exhausted phenotype and tend to have reduced potency. It has been demonstrated that certain features of the apheresis product, such as the predominance of early memory/naïve T cells and low expression of exhaustion markers, correlate with efficacy.[18] It has also been reported that ibrutinib may correct some of the T-cell defects that hinder CAR T-cell production and enhance *in vivo* function.[19] The ability of lenalidomide to enhance CAR T-cell activity has been explored in a mouse model of B-cell lymphoma[20] and provides a rationale for future investigations of the immunomodulatory properties of lenalidomide and its derivatives in CLL.

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