treated (with reasons for not receiving treatment, which are generally available). It is also important to keep in mind that available anti-CD19 CAR T-cell products are only the beginnings of progress in this field and that, together with the addition of B-cell targets other than CD19, CAR T cells will be amenable to modulation of their function to improve efficacy and enhance safety.

The current status of CD19-directed CAR T-cell therapies brings to mind a quote from the late Carroll Shelby, an innovative American automotive designer, who said, "I've always been asked, 'what is my favorite car?', and I've always said 'the next one.'"

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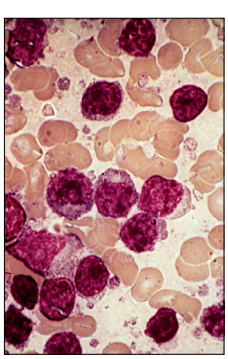
Ibrutinib: searching for a partner drug

Although ibrutinib has become the treatment of choice for patients with relapsed or refractory chronic lymphocytic leukaemia, its position as a first-line regimen is less clear. As ibrutinib prevents homing and migration of leukaemic cells to their microenvironmental niche, it induces quiescence but not apoptosis of chronic lymphocytic leukaemia cells. As a consequence, complete responses are rare and require a prolonged duration of treatment with concomitant high costs, toxicities and side-effects, and the risk of selecting resistant clones.[1–4] For these reasons, and because of its high tolerability and long progression-free survival and overall survival, many physicians still prefer a 6-month regimen of chlorambucil plus obinutuzumab for elderly patients.[5] Improvement of ibrutinib-based therapy can therefore be achieved by reducing side-effects or achieving deep remissions that allow treatment cessation, thereby potentially decreasing the development of resistance. To achieve these desired effects, ibrutinib needs a partner drug. Logical as it sounds, simultaneously combining ibrutinib with rituximab has not shown a progression-free survival benefit,[6] which might be related to the in-vitro observation that ibrutinib inhibits antibody-dependent cellular cytotoxicity.[7] Obinutuzumab might be a more effective alternative because of its higher potency in inducing this cytotoxicity in the presence of ibrutinib.[7]

In *The Lancet Oncology*, Carol Moreno and colleagues[8] present the results of the iLLUMINATE study. They combined ibrutinib with six cycles of obinutuzumab and compared this regimen to standard chlorambucil plus obinutuzumab in patients with untreated chronic lymphocytic leukaemia who were aged at least 65 years, or younger patients with a high cumulative illness rating scale score or a tumour protein p53 mutation. The study ultimately enrolled a fit elderly population in whom the preferred chemoimmunotherapy regimen is arguably bendamustine plus rituximab rather than chlorambucil plus obinutuzumab. Nonetheless, Moreno and colleagues[8] accrued patients remarkably rapidly, with 229 patients enrolled in less than a year, showing the strong interest in chemotherapy-free regimens. With a median follow-up of 31·3 months (IQR 29·4–33·2), iLLUMINATE met its primary endpoint, with significantly longer progression-free survival in the ibrutinib plus obinutuzumab group than in the chlorambucil plus obinutuzumab group (median not reached [95% CI 33·6–non-estimable] *vs* 19·0 months [15·1–22·1]; hazard ratio [HR] 0·23; 95% CI 0·15–0·37; p<0·0001).

Several considerations need to be made. First, as with most chronic lymphocytic leukaemia studies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comparing novel drugs with chemoimmunotherapy, the comparison is between a 6-month time-limited chemoimmunotherapy regimen and continuous treatment. Second, the very healthy elderly population enrolled had few ibrutinib discontinuations (ten [9%] of 113 patients) compared with another report in real-world data (258 [42%] of 621).[3] Despite this low proportion of discontinuations, fatal treatment-emergent adverse events occurred in ten (9%) of 113 patients in the ibrutinib group versus three (3%) of 115 in the chlorambucil group, with no difference in overall survival between the groups. Third, the median progression-free survival of the control group was very short in iLLUMINATE (19·0 months [95% CI 15·1–22·1]) compared with the chlorambucil plus obinutuzumab group in the CLL11 trial (26·7 months),[5] which enrolled less-fit patients with chronic lymphocytic leukaemia with a similar risk profile. Treatment-free duration in the two studies is even more discrepant: at 2·5-year follow-up in iLLUMINATE, 51 (44%) of 116 patients in the chlorambucil plus obinutuzumab group (the control group) had received subsequent treatment whereas median time to next treatment in CLL11 was 51 months. Perhaps these discrepancies are explained by the vigorous radiological assessments in iLLUMINATE. In chronic lymphocytic leukaemia, radiologically detected relapse often occurs long before clinical symptoms develop. A high number of investigations to detect early signs of relapse might unnecessarily lower the bar for initiation of sequential treatment. We therefore encourage the application of the revised International Workshop on Chronic Lymphocytic Leukaemia criteria in clinical trials: one CT scan before start of therapy and a second at final response assessment or at clinically assessed maximal response or relapse.

What is the iLLUMINATE study telling us about obinutuzumab in combination with ibrutinib? Toxicities of ibrutinib are not expected to decrease with use of obinutuzumab. However, obinutuzumab-related side-effects do seem to be mitigated by ibrutinib pretreatment. But does obinutuzumab potentiate the efficacy of ibrutinib? Although the proportions of patients achieving overall responses according to investigator assessment (103 [91%] of 113 patients) with this combination in iLLUMINATE were similar to the proportion in those treated with ibrutinib monotherapy in a previous study (overall response in 125 [92%] of 136 patients), the proportion achieving a complete response according to investigator assessment was higher in iLLUMINATE (46 [41%] patients) than in the previous study (25 [18%] patients).[2] More importantly, the proportion of patients achieving undetectable levels of minimal residual disease (MRD) was higher with the combination than with monotherapy. To identify patients who would benefit more from ibrutinib plus obinutuzumab than either ibrutinib monotherapy or chlorambucil plus obinutuzumab remains challenging, given that overall survival is the ultimate endpoint of interest, short-term and long-term toxicities differ, and patients prefer treatment that does not go on indefinitely. But if the aim is for the duration of therapy to be restricted (a fixed duration or specified stopping point instead of an indefinite maintenance phase) in most patients, an even stronger partner than chlorambucil plus obinutuzumab that more potently induces undetectable MRD is desirable. The BCL2 antagonist venetoclax proved highly active in clearance of chronic lymphocytic leukaemia cells in blood and marrow but less so in lymph nodes,[9] probably because of the abundant expression of additional antiapopototic proteins within the lymph node compartment.[10] Venetoclax is therefore likely to be a well suited partner for ibrutinib. Preliminary data from several ongoing trials of this combination are indeed promising, with high proportions of patients with undetectable MRD, even in high-risk patients. Results from these trials, alongside those of the iLLUMINATE trial, will help elucidate potential future combination drugs for use with ibrutinib in chronic lymphocytic leukaemia.

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Lenalidomide as maintenance for every newly diagnosed patient with multiple myeloma

In patients with newly diagnosed multiple myeloma, how to maintain the responses achieved after optimal therapeutic strategies was a challenge, and maintenance therapy emerged as an option aiming to extend the duration of the response through continued treatment and thereby improving progression-free survival and overall survival. Because maintenance treatment is administered as continuous therapy, emphasis is placed on the convenience of administration, tolerability, and toxicity.[1]

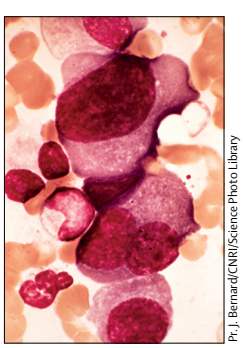
Lenalidomide is the only approved single agent treatment for patients with newly diagnosed multiple myeloma after transplantation.[2] In *The Lancet Oncology*, Graham Jackson and colleagues[3] confirm the benefit of lenalidomide in terms of progression-free survival. In transplantation-ineligible patients, the findings by Jackson and colleagues also support the results reported with low-dose lenalidomide as maintenance after induction with melphalan, prednisone, and lenalidomide, and are in line with the use of full-dose lenalidomide and dexamethasone as continuous therapy reported in the FIRST trial.[4,5] Although the debate in this setting has always been whether to use fixed or continuous therapy, the trend now is use of continuous therapy with either lenalidomide or daratumumab after induction with daratumumab in combination with bortezomib plus melphalan and prednisone.[6]

Lenalidomide maintenance seems to be effective, well tolerated, and convenient, despite the lack of overall survival benefit, because of the influence of rescue therapies in the overall survival. Lenalidomide is, therefore, a maintenance therapy option for every patient with newly diagnosed multiple myeloma, but new therapies or combinations of drugs are needed to improve overall survival in these patients.

Lenalidomide is convenient because it is administered orally, and this study did not report any unexpected toxicity data. Of note, an adequate bone marrow reserve is required for the use of lenalidomide as maintenance treatment and monitoring for second primary cancer is needed. Additional studies assessing health-related quality of life through patient-reported outcomes are necessary to know the patients' perspective.

The approved dose of lenalidomide is 10 mg continuously with the possibility of increasing to 15 mg, but different doses and schedules have been so far used in different trials. In the Myeloma XI trial,[3] the initial dose specified by protocol was 25 mg, but this was changed to 10 mg in a protocol modification. Whether different doses and schedules could potentially result in different outcomes is not known, but the results of this study[3] regarding the median progression-free survival of 26 months (95% CI 22–31) in transplantation-ineligible patients is similar to that reported in the FIRST trial, in which lenalidomide was given at full dose combined with low-dose dexamethasone. Is it, therefore, possible to switch to low-dose lenalidomide without dexamethasone in transplantation-ineligible patients after induction therapy?

New agents or combinations of these are being investigated as maintenance therapy in this setting and might result in new standards of care. For example, vorinostat was combined with lenalidomide in a subset of patients in this study, and we await the results.



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