Ibrutinib—a new standard treatment for mantle cell lymphoma?

In The Lancet, Martin Dreyling and colleagues present the results of a large, international, randomised phase 3 trial comparing the only two drugs approved for mantle cell lymphoma in Europe: temsirolimus and ibrutinib. Among 280 patients, those randomly assigned to daily oral ibrutinib 560 mg (n=139) showed a significant improvement in progression-free survival, the trials primary endpoint, compared with patients (n=141) assigned to daily intravenous temsirolimus 175 mg (1.6 months vs 6.2 months; hazard ratio 0.43 [95% CI 0.32-0.58]). Ibrutinib was also better tolerated than temsirolimus, with fewer study discontinuations because of adverse events. Therefore, the results of this study clearly establish ibrutinib as a new standard for treatment of relapsed mantle cell lymphoma.

Representing only 5% of all non-Hodgkin lymphomas, mantle cell lymphoma (MCL) is not the most epidemiologically relevant disease. Its natural history and poor prognosis, however, have garnered it considerable attention. Following an initial chemotherapy-induced remission of varying duration, patients with MCL undergo a series of subsequent therapies, with successes measured in
months, as the disease and treatment related side effects slowly take their toll. A constant unmet need, MCL has been a model for accelerated development of novel agents. The US Food and Drug Administration (FDA) approved bortezomib and lenalidomide for previously treated MCL based on phase 2 trials that demonstrated response rates of ~30% and equally high rates of study discontinuation due to adverse events.3,4

The development of temsirolimus was less straightforward. Two clinical trials demonstrated that temsirolimus possessed remarkable activity against MCL (with response rates ~40%), but also a therapeutic index that favoured lower doses.5,6 An international phase 3 trial7 compared two doses of temsirolimus against investigator’s choice of treatment (a variety of single chemotherapy drugs), and showed that 22% of patients receiving higher-dose temsirolimus (175 mg per week for 3 weeks followed by 75 mg per week thereafter) achieved an objective response, with a median progression-free survival of 4.8 months, compared with investigator’s choice (2% and 1.0 months, respectively). 22% of patients receiving the higher dose of temsirolimus discontinued treatment because of an adverse event, compared with 11% of patients receiving the investigators’ choice who discontinued for the same reason. These results were sufficient for approval of temsirolimus for the treatment of mantle cell lymphoma by the European Medicines Agency (EMA) in 2008, but not by the FDA.
In 2009, the first-in-class, oral, small molecule inhibitor of Bruton’s tyrosine kinase, ibrutinib, entered clinical development. Based on promising results in seven of nine patients with MCL treated on the phase 1 trial\(^8\), a phase 2 trial (PCYC-1104)\(^9\) was designed with the intention of better evaluating its activity in MCL. The trial, which completed enrollment in March 2012, demonstrated an unexpected response rate of 68% and excellent tolerability profile—9% of subjects stopped treatment due to an adverse event. Ibrutinib was approved by the FDA in November 2013 and by the EMA in October 2014.

Phase 2 trials in oncology can be deceptively convincing. Based on results from a series of promising phase 2 trials of aggressive chemotherapy regimens, use of CHOP (ie, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) to treat large cell lymphoma was almost discontinued until findings from a phase 3 trial proved that this regimen was as effective and better tolerated than its alternatives.\(^{10}\) On the basis of results from a phase 2 trial, patients with mantle cell lymphoma often undergo an intensive regimen designed for acute leukemia.\(^{11}\) Many phase 2 trials have shown the activity of various chemotherapy, immunotherapy, and targeted agents in patients with mantle cell lymphoma. Phase 2 trials also brought outsized hope regarding the activity of temsirolimus in mantle cell lymphoma. The approval of ibrutinib based on results from PCYC-1104 was surprising to everyone other than the participating patients and physicians. By May of 2012 a pivotal phase 2 trial (SPARK; NCT01599949) had been registered, and by July 2012, Dreyling and colleagues’ phase 3 trial
comparing ibrutinib to temsirolimus was registered. In retrospect, these additional studies may appear superfluous, but they also reflect the tremendous speed with which ibrutinib was developed. Many expect that within the next two years ibrutinib will find its way into the front-line setting in combination with standard chemotherapy based on the already completed phase 3 SHINE trial (NCT01776840).

Despite the remarkable progress that ibrutinib represents, mantle cell lymphoma remains incurable. Roughly 30-40% of people with this disease will not respond to ibrutinib, and even among responders relapse seems inevitable. Moreover, patients that experience ibrutinib failure seem to have a poor prognosis: Of the 74 patients that stopped taking ibrutinib in the Dreyling and colleagues’ trial, 44 received subsequent systemic therapy, with eight of 40 assessable patients responding. Fortunately, the mechanisms of resistance to a targeted drug may be minimised, understood, and overcome through rational combinations. Interestingly, the momentum that is carrying ibrutinib forward into front-line combinations with chemotherapy is also shortening the window for phase 1 and 2 trials with rational combinations in the relapsed setting. Hopefully the resources that were mobilised to bring ibrutinib so far, so fast will continue to be available to help us learn how best to use the drug.

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References


