Nature Reviews Clinical Oncology | Published online 31 December 2015; doi:10.1038/nrclinonc.2015.233

HAEMATOLOGICAL CANCER

Targeted agents: efficacy RESONATEs better with fine tuning

> we are witnessing ... a major shift from chemotherapy-based treatments to targeted therapies

In the past few years, the development of agents that inhibit B-cell-receptor signalling has transformed the routine management of chronic lymphocytic leukaemia (CLL). The previous standard of care for patients with CLL of any disease stage was cytotoxic chemotherapy, often in combination with chemoimmunotherapy. Now, three different studies presented at the American Society of Hematology (ASH) Annual Meeting 2015 have explored different options with targeted agents that could improve the treatment of patients with CLL.

Ibrutinib is a first-in-class inhibitor of Bruton tyrosine kinase (BTK), an enzyme critical for B-cell function, and was approved by the FDA in 2014 for the treatment of patients with CLL who had received at least one prior therapy. The aim of the RESONATE-2 trial was to compare ibrutinib with the cytotoxic agent chlorambucil as a first-line treatment for CLL. The patients enrolled in this international phase III trial were at least 65 years of age. Of note, patients aged >65 years are generally not good candidates for intensive intravenous chemotherapy regimens, and the median age at CLL diagnosis is 72 years.

S. Bradbrook/NPG

The relative risks of both progression and death were 87% lower for patients who received ibrutinib ($n = 136$) than for patients in the chlorambucil group ($n = 133$). Treatment with ibrutinib resulted in significantly better response rates, progression-free survival and overall survival, and discontinuation of treatment owing to adverse events was less frequent than with chlorambucil (9% versus 23%). Jan Burger, one of the investigators involved in this trial, declares "ibrutinib, which is well-tolerated in patients over 65 years of age, will hopefully become available as a new standard frontline therapy for patients with CLL."

Ibrutinib can inhibit other kinases in addition to BTK. For this reason, a relatively small number of patients can develop adverse effects during prolonged treatment with ibrutinib. A second-generation BTK inhibitor, acalabrutinib (ACP-196) "has potentially improved efficacy and safety through having more selectivity for the target and a shorter half-life, which allows twice-daily dosing", says John Byrd, who led the development of this agent, as well as ibrutinib.

Byrd and collaborators conducted a phase I/II study to evaluate the safety and efficacy profile of acalabrutinib in 61 patients with previously treated CLL. A high response rate (95%) was observed, and only one case of disease progression occurred after 14 months of follow up. The agent was well-tolerated and only minor adverse events were reported. Byrd explains "these data establish acalabrutinib as a potential improvement over ibrutinib, justifying the ongoing phase III comparison studies."

Bcl-2 is another attractive target in CLL because the expression levels of this antiapoptotic protein are elevated in patients with this malignancy. Early clinical trials of putative Bcl-2 antagonists had disappointing outcomes, but preclinical studies of venetoclax, a novel highly specific agent, produced promising results. Now, a multicentre team led by Andrew Roberts has conducted the first-in-human phase I trial of this agent in patients with CLL.

A total of 116 patients participated in this study, and 79% had an objective response, with 20% achieving a complete response. In addition, treatment was generally well-tolerated, once initial problems with tumour lysis were overcome by careful scheduling. Studies to further evaluate the antitumour efficacy of venetoclax in combination with other agents or in other haematological cancers are underway.

The results of these studies indicate that we are witnessing, in Burger's words, "a major shift from chemotherapy-based treatments to targeted therapies for patients with CLL."

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ORIGINAL ARTICLES Burger, J. A. *et al.* Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N. Engl. J. Med.* **373**, 2425–2437 (2015) | Byrd, J. C. *et al.* Acalabrutinib (ACP-196) in relapsed chronic cymphocytic leukemia. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1509981 | Roberts A. W. *et al.* Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1513257
FURTHER READING Villanueva, M. T. Ibrutinib resonates with us. *Nat. Rev. Clin. Oncol.* **11**, 380 (2014)