EXHIBIT 2016

FRESH FROM THE PIPELINE

Bendamustine

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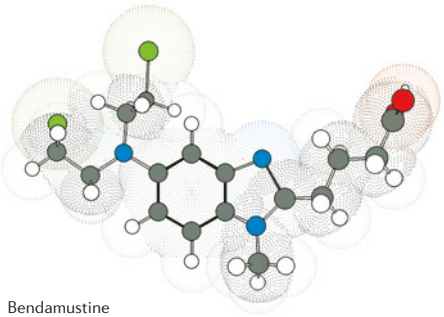


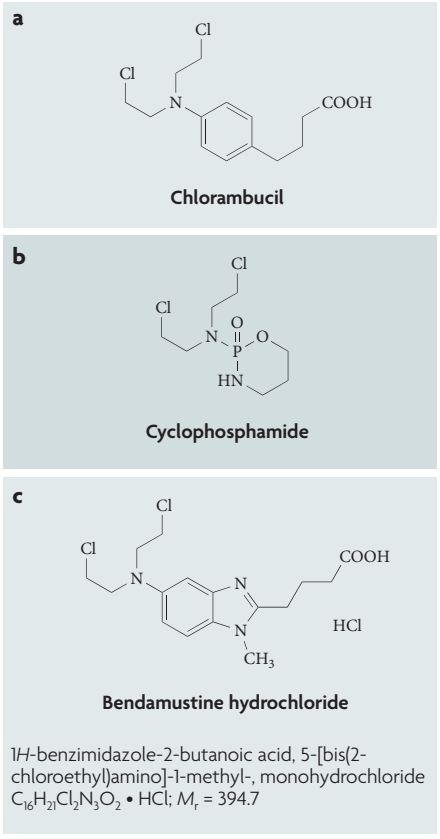
Bendamustine

In March 2008, bendamustine hydrochloride (Treanda; Cephalon), a DNA alkylating anticancer agent, was approved by the US FDA for the treatment of chronic lymphocytic leukaemia.

Chronic lymphocytic leukaemia (CLL), which results from the production of long-lived abnormal lymphocytes, is the most common type of leukaemia in North America and Europe[1]. It mainly affects the elderly, and has a highly variable course, with survival ranging from months to decades[1].

Most patients with CLL are now identified through blood tests that have been performed for unrelated reasons rather than because of signs or symptoms of the disease, and approximately a third of patients never need treatment[1]. Standard management of most patients has therefore traditionally involved a period of watchful waiting to see if the disease progresses[1]. However, there is currently a focus on modifying this strategy as understanding of potential prognostic factors improves[1].

For those patients with CLL who are treated, therapy is generally palliative[1]. Regimens based on DNA alkylating agents such as chlorambucil have been used for decades[1,2]. In the 1980s, purine analogues such as fludarabine were shown to be better at achieving complete remissions than alkylator-based regimens[1,2]. Since then, considerable efforts have focused on developing combination regimes that are built on fludarabine, with some including newer biological therapies such as the B-cell-targeted monoclonal antibody, rituximab (Rituxan; Biogen–Idec/Genentech)[1,2]. Identification of agents with activity against resistant or treatment-refractory CLL has also remained a high priority.



1*H*-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride $C_{16}H_{21}Cl_2N_3O_2 \bullet HCl$; M_r = 394.7

Figure 1 | **DNA alkylating anticancer drugs.** **a** | Chlorambucil. **b** | Cyclophosphamide. **c** | Bendamustine hydrochloride. All three compounds have a 2-chloroethylamine

Basis of discovery

Alkylating agents that exert cytotoxic effects through covalent modification of DNA bases were first introduced as cancer therapies more than half a century ago[3]. Several such agents, including chlorambucil and cyclophosphamide (FIG. 1a,b), are still commonly used, particularly in haematological cancers.

In the 1960s, bendamustine (FIG. 1c) was designed with the aim of creating a bifunctional anticancer agent possessing an alkylating group and also potential antimetabolite properties associated with a benzimidazole ring[4]. It was found to have clinical activity against various cancers, including non-Hodgkin's lymphoma, CLL and multiple myeloma, and was first marketed in Germany in the early 1970s[4]. Interest in the drug for the treatment of CLL has recently been stimulated by clinical trials

cross-resistance with other alkylating agents and fludarabine[4,5].

Drug properties

Bendamustine causes DNA damage that is thought to lead to cell death via several pathways, including apoptosis and mitotic catastrophe[4,6]. A recent study suggests that bendamustine has mechanistic features that differentiate it from other alkylating agents, which might contribute to its efficacy in patients with disease refractory to these drugs[4].

Clinical data

The safety and efficacy of bendamustine were evaluated in an open-label, randomized, controlled comparative trial involving 301 previously untreated patients with Binet Stage B or C (Rai Stages I–IV) CLL requiring treatment[6]. Need-to-treat criteria included haematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy[6].

Patients were randomly assigned to receive either bendamustine hydrochloride (100 mg per m^2, administered intravenously over a period of 30 minutes on days 1 and 2) or chlorambucil (0.8 mg per kg administered orally on days 1 and 15 of each 28-day cycle)[6]. The efficacy end points of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on the National Cancer Institute's working group criteria for CLL[6].

Patients receiving bendamustine showed a higher overall response rate (59%, with a complete response rate of 8%) than patients receiving chlorambucil (26% overall response rate, with a complete response rate of <1%)[6]. For patients receiving bendamustine, median progression-free survival was 18 months, compared with 6 months for patients receiving chlorambucil[6].

Indications

Bendamustine is approved by the FDA for the treatment of patients with CLL[6]. Efficacy relative to first-line therapies other

ANALYSIS | CHRONIC LYMPHOCYTIC LEUKAEMIA

Analysing issues in the treatment of chronic lymphocytic leukaemia is Michael J. Keating, M.B., B.S., Professor of Medicine, Department of Leukemia, MD Anderson Cancer Center, Houston, Texas, USA.

For more than 30 years, the only treatment available for chronic lymphocytic leukaemia (CLL) was the alkylating agents chlorambucil and cyclophosphamide. These drugs were 'grandfathered' in as initial therapy for CLL, and transient control was achieved in approximately half the patients. Fludarabine was then found to be very effective in patients resistant to alkylating agents[7], and it was able to achieve complete remissions, leading to its approval for refractory CLL. Fludarabine has also been compared with chlorambucil in clinical trials as a first-line treatment, but not submitted for approval in this setting.

The monoclonal antibody alemtuzumab (Campath; Genzyme/Bayer) was initially approved for CLL for the treatment of fludarabine-refractory patients where there was no other available option. Recently, alemtuzumab has also been compared with chlorambucil, demonstrating a higher response rate and longer progression-free survival (PFS) in a randomized comparative trial[8], and it is now approved by the FDA as a single agent for first-line therapy.

Bendamustine, which has laboratory evidence to support its activity as a 'better' alkylating agent[4], was approved by the FDA in March this year on the basis of a similar study comparing it with chlorambucil, in which it showed a higher response rate and PFS than chlorambucil[6]. There is extensive experience with bendamustine in Germany and more recently in the rest of Europe, and it has been shown to have activity not only in CLL, but also in a variety of lymphomas alone or combined with rituximab. The chemical structure of bendamustine suggests that it might be a hybrid drug with some purine analogue qualities, although this has not been validated.

While it is refreshing to have new agents with superior activity to chlorambucil in front-line CLL settings available for use in practice, the era of chlorambucil is largely past. It is clear that fludarabine has superior activity to chlorambucil from the point of view of response rate and PFS. However, whether any agent results in improved survival has not been resolved with fludarabine, alemtuzumab or bendamustine. Combinations of purines and alkylators have been demonstrated to be superior to single agents, and combinations of rituximab with fludarabine or fludarabine and cyclophosphamide have led to a dramatic improvement in complete responses and PFS[9,10], although rituximab has not yet been approved for CLL. Long-term studies of such regimens are suggesting that there is an improvement in survival compared with historical experience.

The challenge now in CLL is to establish the best way to introduce these new drugs into clinical practice. For bendamustine, several questions remain, and the lack of peer-reviewed clinical trial data so far is a concern for the academic community. Although it seems clear that bendamustine is a better alkylating agent, it is not yet established whether it will be a major advance when incorporated into combination strategies. For CLL, it is anticipated that bendamustine will be combined with purine analogues and/or monoclonal antibodies, and there is no reason why bendamustine should not establish itself as a significant new agent in lymphoproliferative disorders.

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Box 1 | Market for chronic lymphocytic leukaemia

Analysing the market for therapies for chronic lymphocytic leukaemia are Christian Bach and Uma Yasothan, IMS Health, London, UK.

Chronic lymphocytic leukaemia (CLL) is a slow progressive disease of abnormal white blood cells that occurs predominantly in the elderly. It is estimated that there were ~15,000 new CLL cases diagnosed in the United States in 2007, with more than 75% of those diagnosed over 50 years old and about 4,500 deaths annually[11,12]. At present, there are ~25,000 CLL patients identified as being on active treatment in the United States[13].

At early stages of the disease, an aggressive chemotherapy approach is often not necessary and a 'wait and watch' strategy is typically adopted. For first-line and refractory patients who are treated, a range of options are available, including traditional cytotoxic drugs such as chlorambucil, cyclophosphamide and fludarabine. More recently, the monoclonal antibodies rituximab (Rituxan; Biogen–Idec/Genentech) and alemtuzumab (Campath; Genzyme/Bayer) have been evaluated for CLL alone or in combination with fludarabine-based regimens. In general, monoclonal antibodies such as rituximab have gained wide recognition as useful agents in haematological malignancies.

Bendamustine hydrochloride (Treanda; Cephalon) belongs to the family of drugs known as alkylating agents, and was approved by the US FDA for the treatment of patients with CLL in March 2008. The drug has been designated as an orphan drug in the United States, conferring prolonged market exclusivity. Cephalon in-licensed the drug from Astellas Pharma and will be promoting it in the United States. In Europe, the agent is available under the name of Ribomustin, and is indicated as a single agent or in combination with other anticancer agents for indolent non-Hodgkin's lymphoma, multiple myeloma and CLL. Analysts estimate the initial market potential for bendamustine for CLL in the United States to be $100 million with front line-therapy, which would increase if the drug is subsequently also used in refractory cases and in other combination regimens, for which clinical trials are ongoing.