Ofatumumab in Refractory Chronic Lymphocytic Leukemia: Experience Through the French Early Access Program

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Abstract

The *Autorisation Temporaire d'Utilisation* (ATU) is an early access program available in France for drugs aimed at treating severe diseases not yet covered by a marketing authorization, for patients without any other therapeutic option and who cannot be included in a clinical trial. This report presents the use of single-agent ofatumumab in 30 patients with advanced chronic lymphocytic leukemia in the French ATU program.

Background: The *Autorisation Temporaire d'Utilisation* (ATU) is an early access program available in France for drugs aimed at treating severe diseases not yet covered by a marketing authorization, for patients without any other therapeutic option and who cannot be included in a clinical trial. **Patients and Methods:** This report presents the use of single-agent ofatumumab in 30 patients with advanced chronic lymphocytic leukemia (CLL) in the French ATU program. **Results:** These very-high-risk patients had received multiple previous treatments (median = 6), and most had disease that was fludarabine-refractory or alemtuzumab-refractory (or both) or was unsuitable for alemtuzumab treatment. In the intent-to-treat analysis, the overall response rate was 47% (4 of 30, complete response; 10 of 30, partial response). Of 13 patients with 17p deletion, 6 displayed response to ofatumumab, including 2 complete responses. Treatment was well tolerated, with 17 grade 3 or 4 adverse events; 4 cases of grade 3 or 4 infusion reactions were reported, with favorable immediate outcome. Among nonhematologic complications, infections were the most frequent. **Conclusion:** The results confirm the efficacy and acceptable tolerability profile of ofatumumab as a single agent in severely ill patients with CLL. Attention should be paid to possible early infusion reactions to ofatumumab, as well as to the risk of infection.

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Introduction

Chronic lymphocytic leukemia (CLL) is a blood disorder defined by a neoplastic proliferation of mature B cells characterized by a specific CD5-positive and CD23-positive phenotype in the blood, bone marrow, and secondary lymphoid organs (lymph nodes and spleen). It is the most common adult leukemia in Western countries, accounting for about 30% of all leukemias. In France, nearly 4500 incident cases of CLL/small lymphocytic lymphoma were estimated in 2012, 60% in male patients. The average age at diagnosis was 71 years in men and 74 years in women.[1]

In 2010, over 1000 deaths were attributable to the disease.[2] Its prognosis is heterogeneous: some patients have a prognosis that is not

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modified by the disease, whereas others die of the disease or infectious complications early after diagnosis. The 5-year survival rate, all stages combined, is greater than 70%. However, survival is much poorer in patients with high-risk disease, in particular those with unfavorable cytogenetic status (ie, deletion of the *TP53* locus in 17p) and those with disease refractory to fludarabine. Thus, there is a need for new treatments with activity in relapsed or refractory disease.

Ofatumumab (Arzerra) is a type I human monoclonal antibody that binds to a different epitope of CD20 than rituximab. Complement-dependent cytotoxicity appears to be greater than with rituximab, even at lower density of CD20 on the cell surface. In vitro, ofatumumab is more effective than rituximab in killing CLL cells, which are considered relatively resistant to rituximab because of their low expression of CD20.[3] Moreover, ofatumumab was found to be more efficient than rituximab in lysing B CLL cells in whole blood and in combination with chemotherapy.[4]

The French early access program described herein was made available before the marketing authorization of ofatumumab. In France, this kind of program is called ATU, which stands for *Autorisation Temporaire d'Utilisation* (Temporary Authorization to Use). It has been set up by and is controlled by the French drug authority, ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé); it is applicable to drugs aimed at treating severe diseases not yet covered by a marketing authorization, for patients without any other therapeutic option and who cannot be included in a clinical trial.[5] Ofatumumab nominative ATUs were granted by the ANSM between November 2009 and July 2010. On April 19, 2010, the European Commission issued a conditional marketing authorization valid throughout the European Union for ofatumumab. The decision was based on the favorable opinion of the Committee for Medicinal Products for Human Use.[6]

Patients and Methods

This early access program was opened on a named-patient basis. Each request for treatment was to be submitted by a hematologist to the ANSM for individual authorization. Upon the agreement of the ANSM, the drug was sent to the hospital pharmacist by the pharmaceutical company developing ofatumumab, so that the treatment could be administered to the patient under the physician's responsibility. Physicians were committed to collect safety information and to report immediately any severe or unexpected adverse events (AEs) to the ANSM drug safety centers.

A total of 34 requests were submitted by treating physicians and evaluated and accepted by the French authorities. Because of the severity of their disease, 2 patients died before starting treatment with ofatumumab. All patients were informed by their treating physician about ofatumumab and the specific status of the drug in this early access program. In total, 32 patients, followed up in 13 French hematology centers, were able to receive ofatumumab. The present authors could retrieve information in the patient files for 30 of the 32 patients.

Ofatumumab was administered according to the approved regimen: 8 weekly, then 4 monthly intravenous infusions of ofatumumab (dose 1, 300 mg; doses 2-12, 2000 mg). Patients were premedicated 30 minutes to 2 hours before infusion with intravenous corticosteroids, analgesics, and antihistamine.

The efficacy and safety data reported here were collected retrospectively within patient medical files through a questionnaire completed in 2013 by each participating physician. The collected information was patient demographic data, age and stage at diagnosis, cytogenetic status, previous treatments (number, type, and outcome), disease stage and standard hematology at ofatumumab initiation, and hematologic and nonhematologic toxicity of ofatumumab. Regarding safety, causality assessment was not collected systematically. AEs were graded by the treating physicians according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The efficacy data retrieved were objective response (OR) according to the National Cancer Institute Working Group criteria for CLL[7] as reported by the treating physicians, progression-free survival (PFS) defined by the physician as the interval between the first treatment day to the first sign of disease progression, and overall survival (OS). OR and AEs are reported through descriptive analyses. PFS and OS were evaluated using Kaplan-Meier estimates.

Results

The baseline characteristics of the 30 patients are reported in Table 1. Before starting ofatumumab treatment, most patients had advanced disease; 12 (40%) had bulky disease, 24 (80%) were in Binet stage C, and 12 (40%) had Eastern Cooperative Oncology Group (ECOG) performance status 2 or 3. Of 30 patients, 24 had cytogenetic analysis, which displayed a majority of 17p deletions [del(17p)] (54%), followed by 11q deletions [del(11q)] (25%).

The pretreatment status of the patients is reported in Table 2. All patients received at least 1 dose of ofatumumab, and 77% of them received at least 8 cycles. The median number of cycles given

Table 1 Pretreatment Characteristics of Patients (Before Receiving Ofatumumab Through the French Nominative ATUs)

Characteristic	Value (n = 30)
Gender (M/F)	21/9 (70%/30%)
Age (years) at Diagnosis, Mean (Range)	58.5 (45-78)
Time (years) Since Diagnosis, Median (Range)	8.0 (1.0-19.1)
Age (years) at First Ofatumumab Cycle, Mean (Range)	66.7 (50-86)
No. of Prior Treatment Regimens, Median (Range)	6 (1-9)
No. of Patients Pretreated With Rituximab	24 (80%)
No. of Patients Pretreated With Fludarabine	25 (83%)
No. of Patients With Fludarabine-Refractory Disease	15/25 (60%)
No. of Patients Pretreated With Alemtuzumab	22 (73%)
No. of Patients With Alemtuzumab-Refractory Disease	15/21 (71%)
No. of Patients With Fludarabine- and Alemtuzumab-Refractory Disease	7 (23%)
Fludarabine or Alemtuzumab Contraindication	4 (13%)
No. of Patients Treated by Stem Cell Transplant	7 (23%) Autologous, 4 Allogeneic, 3

Abbreviation: ATU = Autorisation Temporaire d'Utilisation.