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LETTER TO THE EDITOR

Correspondence in reference to previously published manuscript: "Faouzi Djebbari et al. Efficacy and infection morbidity of front-line immuno-chemotherapy in follicular lymphoma. Eur J Haematol. 2020; 105: 667-671"

To the Editor

Rituximab and cyclophosphamide-containing regimens (cyclophosphamide, vincristine, and prednisone with or without doxorubicin) had been predominantly used as standard immunochemotherapy for symptomatic indolent B-cell lymphomas (i-BCLs) until the recent introduction of bendamustine plus rituximab schedule.[1] However, the increased incidence of opportunistic infections following bendamustine exposure has raised questions regarding its safety and widespread adoption.[2]

We read with great interest Djebbari et al's study in the July 2020 issue number 5 of *European Journal of Haematology*.[3] This retrospective study assessed 3-year infection morbidity of newly diagnosed follicular lymphoma (FL) patients treated with immunochemotherapy regimens, including anti-CD20 monoclonal antibodies (mAbs), *that is*, rituximab (R) or obinutuzumab (O) plus bendamustine (BR [n = 32] and OB [n = 9], respectively) eventually followed by anti-CD20 mAb maintenance (in 31 of them) in the 2009-2019 period in the Oxford's Tertiary Haematology Center of UK. Overall, 26/41 patients (63%) experienced at least one infection of grade ≥1 with a total of 23 episodes of high-grade documented infections. Moreover, 16 infection-related admissions during induction and 7 infection-related admissions during maintenance were recorded (grade: 3-5). Thus, during the 3-year infection follow-up, bendamustine-based regimens led to a high rate of patients experiencing any grade of infection and a high number of infection-related admissions. The authors underscore that these findings influence decision-making across different frontline FL therapeutic approaches. There is the need of interventions that could mitigate the infectious toxicity (including granulocyte colony-stimulating factors [G-CSFs] and prophylactic antimicrobials) to establish the full value of frontline treatment with BR schedule in patients with i-BCLs in real life.[1,4]

In *Supportive Care Cancer* of 2017,[5] we reported encouraging single-center safety results of a prospective trial in 61 adult patients receiving firstline BR therapy and pegfilgrastim prophylaxis (BR-Peg group) for i-BCLs (including follicular lymphoma for 68.8% of patients) during the 2014-2016 period in Italy. All patients systematically underwent 6 mg pegfilgrastim (Neulasta®; Amgen) injected subcutaneously in a single administration on day 4 of each 4-week cycle of BR, from the first course of immunochemotherapy until the last course. During 6 months of follow-up from the start of immunochemotherapy, BR-Peg regimen was associated with a rate of incidence of infections (including febrile neutropenia [FN] and pneumonia) and hospitalizations required for FN complications of 11.4% and 4.9%, respectively. We then carried out a single-center interventional prospective trial, with similar target population of *Djebbari et al*, in 67 patients (median age: 63 years) with FL. From January 2016 to January 2020, according to our institution guidelines, consecutive symptomatic patients with FL received frontline BR, intensified primary antimicrobial prophylaxis (IPAMP), and R-maintenance (if needed). Preliminary results were published in *haematologica* of 2019[6]; here, we report the mature results from this study characterized by a specific intervention against infections, *that is*, the IPAMP scheme consisting of long-acting pegfilgrastim (6 mg, s.c) or lipegfilgrastim (6 mg, *s.c*) on day 4 of each BR cycle (as above described), and trimethoprim-sulfamethoxazole (960 mg bid die, twice a week) and acyclovir (400 mg bid die) from day 1 until 6 months after the last BR cycle. All patients had IPAMP treatment systematically as scheduled, and no modifications were made. With a median follow-up of 23 months, the rate of infections was 6% (including pneumonia [1 case], bloodstream infection [1 case], and gastrointestinal tract infection [2 cases]), and the rate of infection-related hospitalizations was 3% (2/67 patients).

With the systematic, prompt and sustained use of our vigorous primary anti-infectious prophylaxis (pegfilgrastim/lipegfilgrastim, trimethoprim-sulfamethoxazole, and acyclovir), we were able to drastically bring down the rate of infections and hospitalizations required for infectious complications in patients with i-BCLs receiving BR regimen during the first two years of therapy (Table 1). Studies from other institutions with a longer follow-up are needed to assess the late infectious risk following the BR therapy, especially from opportunistic microorganisms, possibly due to prolonged T-cell depletion.[1]

TABLE 1 Infection outcomes for frontline bendamustine plus anti-CD20 mAbs according to the standard schedule[a] in patients with follicular lymphoma (FL) and/or other indolent B-cell lymphomas (i-BCLs), reported by the three trials analyzed in the present manuscript

Author, year	Type of study	Type of underlying hematological disease (number of cases)	Median age, (range)	Features for start immunochemotherapy (percentage of patients)	Antimicrobial prophylaxis (percentage of patients)	Nadir, ANC cells/ul, median count (range)	Outcomes reported
Djebbari et al, 2020[3]	Retrospective (single-center)	FL, 41	56 y (28-83)	Ann Arbor stages III-IV (98) Anemia (27) Bone marrow involved (63) LDH > 240 U/L (39) FLIPI intermediate/high risk (71)	Acyclovir (100) G-CSF (22)	1900 (0-6100)	Infections, 63.4% (including all grades)[b] High-grade documented infection episodes, 23; Deaths from infection, 2
Cerchione et al, 2017[5]	Prospective (interventional, single-center)	FL, 42 i-BCLs, 19	45.4 y (33-77)	Ann Arbor stages III-IV (98) B symptoms (31) Bone marrow involved (69) Extranodal involvement (74) LDH > 240 U/L (34) FLIPI intermediate risk (31) FLIPI high risk (57)	Primary prophylaxis with pegfilgrastim (100)	1734 (880-2110)	Infections, 11.4% (including FN, 2 cases; FN with clinically documented infection at the lower respiratory tract, 3 cases; FN with microbiologically documented infection, 2 cases [1 Gram-positive, 1 serum CMV-DNA positivity]; Infectious complication-related hospitalizations, 4.9%. Chemotherapy disruptions, 1.6%
Giordano et al, 2019[6]	Prospective (interventional, single-center)	FL, 67	63 y (60-82)	Ann Arbor stages III-IV (90) B symptoms (31) Bulky disease (30) Bone marrow involved (59) Extranodal involvement (70) FLIPI intermediate risk (41) FLIPI high risk (60)	Primary prophylaxis with long acting G-CSF, trimethoprim-sulfamethoxazole, and acyclovir (100)	1646 (980-2990)	Infections, 6% (including FN with clinically documented infection at the lower respiratory tract [1 case] and gastrointestinal tract [2 cases]; FN with microbiologically documented infection, 1 case [bacteremia due to Gram-negative]; Infectious complication-related hospitalizations, 3%. Chemotherapy disruptions, 3%

Note: Primary antimicrobials prophylaxis: pegfilgrastim/lipegfilgrastim (6 mg, *s.c.*) on day 4 of each immunochemotherapy cycle (from the first until the last 4-wk cycle); trimethoprim-sulfamethoxazole (960 mg bid die, twice a week) and acyclovir (400 mg bid die) from day 1 until 6 mo after the last cycle in all patients.

Stage III, defined as multiple lymph node groups on both sides of the diaphragm; stage IV, defined as multiple extranodal sites or lymph nodes and extranodal disease.[2]

FLIPI score. Five factors included were as follows: age older than 60 y, serum lactate dehydrogenase (LDH) above normal, Ann Arbor stage III or IV, nodal involvement at more than 4 sites, and hemoglobin level <12 gr/dL. Each factor gets 1 point, and possible scores range from 0 to 5. A higher score indicates poorer prognosis.[2]

ANC, absolute neutrophil count.

G-CSF, granulocyte colony-stimulating factors.

FN, febrile neutropenia is one of the most important clinical signs of infection during chemotherapy treatment and is characterized by an absolute neutrophil count (ANC) <1000/mm^3 and at least one temperature measuring of ≥38°C.

mAbs, monoclonal antibodies.

Chemotherapy disruptions: If the leukocyte count was less than 2000/mm^3 before a scheduled cycle, treatment cycle was delayed for at least 1-wk (time disruption), or bendamustine dose was reduced to 70 mg/m^2 if leukocyte count less than 1000/mm^3 was noted on two consecutive days between cycles (dose disruption).

[a]Immunochemotherapy treatment included intravenous bendamustine (90 mg/m^2 given over 30-60 min on days 1 and 2 of each cycle) plus rituximab (375 mg/m^2 on day 1 of each cycle), every 4 wk for up to 6 cycles[2] in the Cerchione et al's study[5] and Giordano et al's study[6]; in the Djebbari et al's study[3] 32 patients received rituximab-bendamustine, while 9 patients received obinutuzumab-bendamustine (number of cycles and dosages are not reported).

[b]According to the Common Terminology Criteria for Adverse Events (version 4).

KEYWORDS

antimicrobial prophylaxis, bendamustine, indolent lymphoma, rituximab

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