

BTK Inhibitors and Dexamethasone-Rituximab-Cyclophosphamide Are Associated with Lower Rates of Infections and Infection-Related Hospitalizations Compared with Bendamustine-Rituximab in Waldenström Macroglobulinemia: A Multicentre Real-World Study.

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Infections are a major cause of morbidity and mortality in patients with Waldenström Macroglobulinemia (WM). Over recent years, the use of Bruton's Tyrosine Kinase inhibitors (BTKis) has increased in WM, with the perception of reduced infection rates. However, available data are largely derived from clinical trials, and real-world evidence remains scarce.

This study aimed to describe infectious complications in patients with WM treated with chemo-immunotherapy (CIT) or BTKis in a real-world setting, evaluating infection incidence during first- and second-line treatment according to the timing of onset.

This retrospective multicentre study included 496 patients diagnosed with WM and treated since 2008 across 13 Italian hematology centres.

In the first-line setting, treatments included bendamustine-rituximab (BR, n=169), dexamethasone-rituximab-cyclophosphamide (DRC, n=150), other CIT regimens (n=62), rituximab or steroids alone (n=54), chemotherapy alone (n=40), and BTKis (n=21). A total of 116 infections were recorded. Infection rates at 0–6, 6–12, 12–18, and 18–24 months were: BR 16%/5%/3%/3%, DRC 10%/3%/1%/0%, and BTKis 5%/7%/0%/0% (Figure 1A). Thirty-five infections (30.2%) required hospitalization, with rates of BR 6%/2%/1%/1%, DRC 1%/1%/0%/0%, and BTKis 0%/0%/0%/0% (Figure 1B).

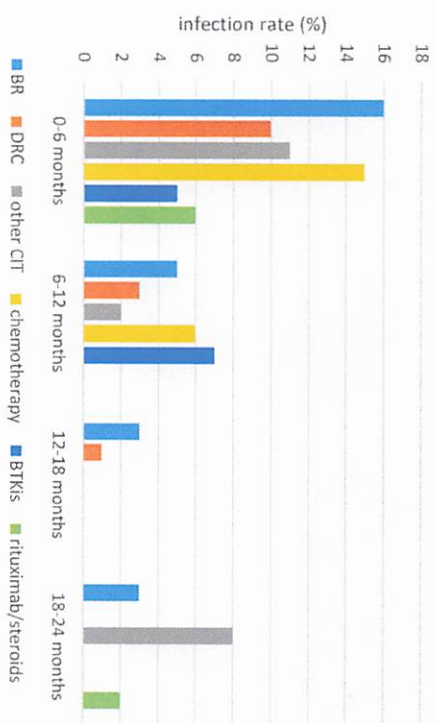
In the second-line setting, 214 patients received subsequent therapies: BTKis (n=111), BR (n=24), DRC (n=15), bortezomib-based regimens (n=20), chemotherapy (n=24), and rituximab alone (n=20). A total of 76 infections were observed. Infection rates at 0–6, 6–12, 12–18, and 18–24 months were: BR 17%/5%/5%/0%, DRC 0%/0%/0%/0%, and BTKis 10%/7%/13%/2% (Figure 1C). Twenty-six infections (34.2%) resulted in hospitalization, with rates of BR 12%/0%/5%/0%, DRC 0%/0%/0%/0%, and BTKis 3%/3%/2%/0% (Figure 1D).

Overall, infection rates were similar between first- and second-line treatment within each regimen, except BTKis. In first line, BTKis were associated with lower infection rates than BR and DRC during the first 6 months, similar rates between 6 and 12 months, and no infections beyond 12 months. No

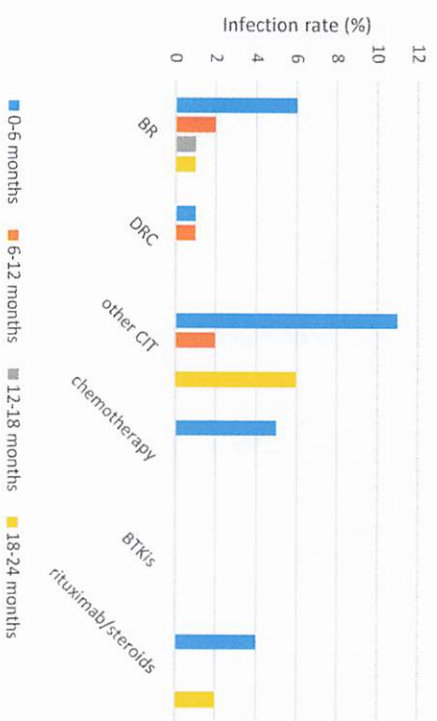
infection-related hospitalizations occurred with BTKis, whereas hospitalization rates remained low with BR (except during the first 6 months, 6%) and DRC. Among CIT regimens, DRC showed the lowest infection rates, with no infectious events in second line. In relapsed/refractory WM, BR showed higher infection rates than BTKis during the first 6 months, whereas BTKis had higher rates between 6–12 and 12–18 months. Hospitalization rates remained low with both regimens, except for BR during the first 6 months (12%).

This large retrospective real-world study highlights the favourable infectious safety profile of BTKis, particularly in the first-line setting, where they were associated with numerically lower infection rates without infection-related hospitalizations in this retrospective cohort. Among CIT regimens, DRC also emerged as a well-tolerated alternative with a low risk of infectious complications. In relapsed/refractory WM, infections remained infrequent but were more common during the first 18 months of BTKi therapy, supporting closer monitoring and appropriate prophylaxis during this period. These findings support BTKis as a preferred frontline strategy from an infectious safety perspective. Future studies should determine whether earlier use of BTKis and fixed-duration BTKi-based combinations can maintain the favourable infectious profile observed with continuous BTKi therapy in second-line.

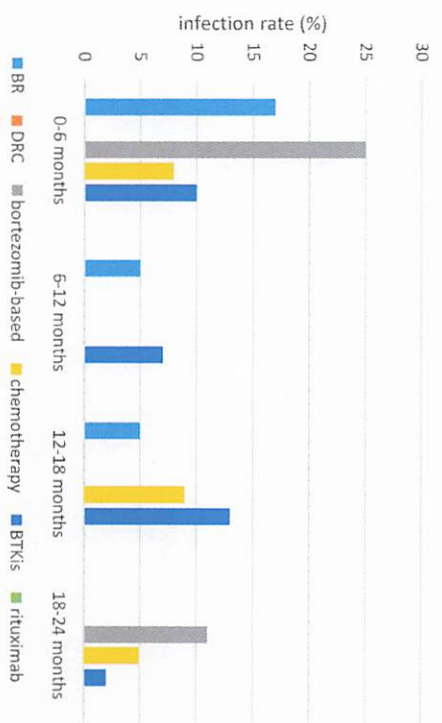
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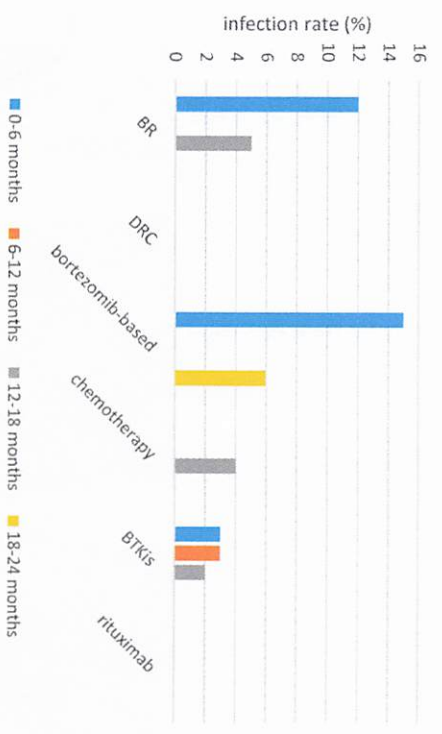
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