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Rituximab maintenance in elderly patients with follicular lymphoma

Follicular lymphoma (FL) is a chronic, indolent lymphoid malignancy and represents the most common slow growing lymphoma in the United States and Europe [1]. Patients with FL experience generally favorable outcomes with median overall survival (OS) lasting close to 18 years [2]. Improvements in FL survival have occurred consistently over the past several years, and for symptomatic patients treated with chemoimmunotherapy, durable disease control is achievable, lasting several years. Chemo-immunotherapy with antiCD20 antibody rituximab has changed the treatment landscape of FL by improving response rates and progression free survival (PFS). As such, extending response duration and minimizing time to next treatment with rituximab maintenance have become priorities in this indolent disease [3]. The PRIMA study identified the benefit in PFS for patients with FL treated after chemo-immunotherapy, though without an advantage in overall survival (OS). Rituximab maintenance is typically administered every 2 months for a total of 2 years. Ten year long term follow up from the PRIMA study showed the PFS benefit was sustained, with approximately half of patients remaining progression free, but still without a change in OS [4].

Belada and colleagues from the Czech Lymphoma Study Group report on real world outcomes of patients with FL over the age of 65 treated with either chemo-immunotherapy followed by observation, or chemo-immunotherapy followed by rituximab maintenance. They demonstrated that the use rituximab maintenance led to improvements in OS (5 year OS 83.7%) compared to those observed after chemoimmunotherapy (5 year OS 64.3%). Moreover on multivariate analysis they identified 62% reduction in risk of progression and 53% reduction in risk of death with the use of rituximab maintenance, though the use of retrospective data suggests caution in the interpretation of these findings. Patients who most benefitted appeared to be those who had either complete response (CR) or unconfirmed complete response (Cru) by CT criteria. Additionally those treated with R-CHOP seemed to have better response rates and fewer rates of progression compared to patients treated with other regimens, consistent with previous literature [5]. The observed benefit from rituximab may be due to fewer patients receiving maintenance with concern for refractory disease, or based on more favorable disease biology leading to better disease control. In addition, practices on the use and implementation of rituximab maintenance vary in the Czech Republic, and the use of PET scans for assessment of disease response (considered standard in many centers) [6] is not uniform.

Other analysis have provided variable results on maintenance rituximab following more contemporary chemotherapy regimens. On the BRIGHT study, after front line bendamustine and rituximab (BR), maintenance did improve PFS and had a trend towards improved OS [7]. In the randomized StiL study however, OS benefit was not observed following BR [8]. The GALLIUM study testing obinutuzumab based induction in FL followed by maintenance suggested detriment to select subsets of patients [9]. A higher number of fatal adverse events were reported in FL patients treated with bendamustine compared with CVP or with CHOP but importantly, these were observed in patients treated with bendamustine during maintenance obinutuzumab or rituximab. Notably, these were more likely to occur in elderly patients. While the current work by the Czech Lymphoma Study Group did not include patients treated with bendamustine, it highlights important considerations to prolonged therapy in vulnerable individuals.

Elderly patients with FL (> 70 years old) seem to have similar disease outcomes compared to younger patients based on a recent analysis of the Follicular Lymphoma Analysis of Surrogate Hypotheses (FLAHS) Group Study of over 5000 patients [10]. However in The National LymphoCare Study analysis of very elderly patients (> 8o years old), inferior outcomes were observed compared to younger patients, and many patients continue to experience death from disease. Baleda's work contributes importantly to a paucity of literature on maintenance therapy in elderly patients with FL. However taken together, the available data on this topic suggest that maintenance rituximab should be used with caution for older patients and should be decided with consideration to induction therapy used. In the absence of strong survival benefit noted in prospective randomized trials and the potential for morbidity, the role of maintenance should be limited to select patients such as those patients not receiving bendamustine based induction, those with limited comorbidity, and those with adequate response to treatment.

Conflict of interest

None.

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