Best Practice & Research Clinical Haematology xxx (2017) 1–8

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Management of untreated advanced stage follicular lymphoma: Role of patient discernment

Jayadev Manikkam Umakanthan, Mathew A. Lunning*

Division of Hematology & Oncology, Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, 986840, Nebraska Medical Center, Omaha, NE 68198-7680, United States

ARTICLE INFO

Article history:
Received 2 October 2017
Accepted 23 October 2017

Keywords:
Follicular Lymphoma
Advanced stage
Treatment

ABSTRACT

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma. Advanced stage disease is common at diagnosis. The timing of treatment for follicular lymphoma is best approached by considering the combination of presence or absence of symptoms along with estimation of tumor burden. Upfront treatment strategies should take into initial presentation variables, pace of disease progression and goals of care after discussion with the patient. Treatment approaches remain diverse and patient discernment is paramount.

1. Introduction

In the era of digital medicine where vast amount of information is available at a click, the main role of the treating physicians is to assimilate this enormous knowledge to best fit the patient sitting in front of them. This becomes a complex task in a disease as Follicular Lymphoma (FL) where more than one option is considered ideal or reasonable, based on the viewpoint. The decision of when to treat is as important as how to treat this indolent lymphoma. In this review, we summarize the presently available evidence to guide the optimal management of untreated FL, with a focus on trying to answer the questions of when and how.

2. Advanced stage FL - placing the patient in the right box

In advanced stage FL, the question of when to treat is best approached by considering the combination of presence or absence of symptoms along with estimation of tumor burden using the GELF criteria [1]. This relies heavily on the fact that advanced stage FL remains an indolent, but incurable disease with the presently available therapies. Major clinical trials comparing different chemotherapy regimens have historically used GELF criteria as a discriminating factor for assigning patients to different arms [2,3]. In the original GELF study, patients estimated to have low tumor burden using a set of criteria (Table 1), were randomized to watchful waiting (WW) vs treatment with either prednimustine or interferon alpha. The results showed that WW was not inferior to early treatment in patients with low tumor burden determined by GELF criteria [4]. Since then, subsequent clinical trials evaluating chemo-immunotherapy in FL have included meeting high tumor burden by

* Corresponding author.
E-mail address: mlunning@unmc.edu (M.A. Lunning).

https://doi.org/10.1016/j.beha.2017.10.004
1521-6926/

Please cite this article in press as: Umakanthan JM, Lunning MA, Management of untreated advanced stage follicular lymphoma: Role of patient discernment, Best Practice & Research Clinical Haematology (2017), https://doi.org/10.1016/j.beha.2017.10.004

Table 1
GELF criteria for high tumor burden.

GELF CRITERIA
Any Nodal or extra-nodal tumor mass with a diameter >7 cm
Involvement of greater than three nodal sites with a diameter > 3 cm
Systemic symptoms
Substantial Splenomegaly
Serous effusions
Local risk of compression (epidural, ureteral, etc)
Leukemia or blood cytopenia

GELF criteria as a requirement for inclusion to the treatment arm. What we do not know entirely is how the low tumor burden population may fare with modern treatment options such as R-chemotherapy.

Hence, in the absence of paucity of data, we can consider treatment for advanced FL either when a patient is symptomatic or has estimated high tumor burden by GELF criteria. This along with the assessment of the vital factors of age, performance status, comorbidities and disease related anxiety dictates management as to timing and choice of therapy. Thus, the first step in the management of a patient with FL is placing the patient in the right box.

	High Tumor Burden	
Symptoms	+/+	+/−
	−/+	−/−
Vital Factors		
Age		
Performance status		
Comorbidities		
Disease related anxiety		

3. Asymptomatic/low tumor burden

The question of when to treat is probably most relevant and highly debated in this sub-group. First advocated by Stanford [5], numerous studies since then have established WW as an acceptable strategy for these patients without any inferior results [4,6–8]. But, the caveat is that most of these studies were conducted in the pre-rituximab era and hence we do not know how the survival prolongation effects of rituximab (R) with combination chemotherapy affects the natural history of the disease in this population. However, given that, the present therapies for FL remain non-curative, WW holds relevance and retains its place in the asymptomatic low tumor burden population. However, monotherapy with single agent rituximab has been tested in this population by Ardeshna et al. [9] In this British study, patients with low-tumor-burden FL were randomly assigned to three groups: 1) WW 2) rituximab induction along weekly for 4 weeks and 3) rituximab induction followed by maintenance rituximab every 2 months for 2 years. Rituximab induction alone group was closed early due to slow accrual and the study was amended to a two-arm study. Median follow-up was 46 months in the two-arm study and 50 months in the three-arm study. At 3 years, 88% of the rituximab maintenance group vs 46% of the WW group had not needed further treatment (hazard ratio [HR] = 0.21, P < .0001). No treatment was needed by 78% of patients in the rituximab induction group, which was significantly better than the WW group (HR = 0.35, P < .0001). There was no difference in time to next treatment between the induction alone vs induction followed by maintenance group (HR = 0.75, P = .33) but the amended trial was underpowered for the comparison of the two groups. There was no difference in OS benefit between any of the groups.

Martinelli et al. reported the results of a long-term cohort of patients with FL treated with single-agent rituximab administered with a prolonged schedule [10]. In this study, previously untreated patients responding to rituximab induction (n = 38) had the best outcome: 45% were still alive without disease progression at 8 years, hence not requiring chemotherapy. However, this subset of population is too small to draw definitive conclusions but may suggest towards the benefit of early rituximab therapy followed by prolonged exposure that helps to keep chemotherapy on the shelf longer.

The RESORT trial tested the concepts of maintenance rituximab (MR) vs rituximab re-treatments (RR) upon progression following initial induction therapy [11]. Time to treatment failure was not different between the two groups: 3.9 years for patients receiving RR vs 4.3 years for those receiving MR (P = .54) with three-year freedom from cytotoxic therapy of 84% vs 95% (P = .03), respectively. Of note, the median number of rituximab doses for patients receiving RR was four Vs eighteen for those receiving MR, pointing towards conservative resource utilization in the re-treatment group. There was no difference in health-related quality of life (HRQOL) between the two groups. Grade 3 to 4 toxicities were infrequent in both arms.

In an interesting study from the Princess Margaret Cancer Centre, Prica et al. performed cost analysis of rituximab monotherapy in asymptomatic, advanced FL patients. They used a Markov decision analysis model over a lifetime horizon to compare the cost utility of rituximab induction and maintenance to induction alone and a WW approach. All patients were modeled to receive treatment upon progression with bendamustine plus rituximab followed by 2 years of rituximab

Please cite this article in press as: Umakanthan JM, Lunning MA, Management of untreated advanced stage follicular lymphoma: Role of patient discernment, Best Practice & Research Clinical Haematology (2017), https://doi.org/10.1016/j.beha.2017.10.004