Leukemia Research 73 (2018) 29–38

Contents lists available at ScienceDirect

Leukemia Research

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

Research paper

The influence of maintenance therapy of rituximab on the survival of elderly patients with follicular lymphoma. A retrospective analysis from the database of the Czech Lymphoma Study Group

David Belada[a,*], Vit Prochazka[b], Andrea Janikova[c], Vit Campr[d], Petra Blahovcova[e], Robert Pytlik[e], Alice Sykorova[a], Pavel Klener[e], Katerina Benesova[e], Jan Pirnos[f], Juraj Duras[g], Heidi Mocikova[h], Marek Trneny[e]

[a] 4th Department of Internal Medicine - Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic
[b] Department of Hematology, University Hospital Olomouc, Olomouc, Czech Republic
[c] Department of Internal Medicine – Hematology and Oncology, Masaryk University and University Hospital Brno, Brno, Czech Republic
[d] Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University and Faculty Hospital in Motol, Prague, Czech Republic
[e] 1st Department of Medicine, First Medical Faculty, Charles University and General University Hospital, Prague, Czech Republic
[f] Department of Oncology, Hospital Ceske Budejovice, Ceske Budejovice, Czech Republic
[g] Department of Clinical Hematology, Teaching Hospital Ostrava, Ostrava, Czech Republic
[h] Internal Clinic of Haematology, University Hospital Kralovske Vinohrady, Prague, Charles University in Prague, 3rd Faculty of Medicine, Prague, Czech Republic

ARTICLE INFO

Keywords:
Follicular lymphoma
Elderly patients
Rituximab
Immunochemotherapy
Maintenance
Survival

ABSTRACT

The rituximab maintenance (RM) therapy for follicular lymphoma is effective and clinically well tolerated, however there is limited data regarding this from the elderly segment of the population. This analysis was performed to evaluate the efficacy of RM in elderly patients 65 years of age and older and to assess the influence of the induction therapy with immunochemotherapy (R-CHEMO) on the treatment outcome in a real world setting. A total of 232 consecutive patients treated with first-line R-CHEMO and RM (RM1 group; n = 158) or observation (RM0 group; n = 74) were analyzed. The effect of which induction therapy (R-CHOP vs. R-CVP) and the response of the patients to the first-line therapy were also evaluated. The addition of RM improved the treatment results in elderly patients. The 5- year overall survival rate in patients receiving R-CHEMO + RM1 compared to patients receiving R-CHEMO + RM0, was 83.7% (95% CI 76.1–89%) and 64.3% (95% CI 51.8–74.3%), respectively, p = 0.0012. The induction therapy with R-CHOP was found to be more effective than R-CVP but it is necessary to point out higher age of patients in the R-CVP arm. The 5- year overall survival rate in patients using R-CHOP ± RM and R-CVP ± RM was 84.9% (95% CI 77.5–90%), and 65.0% (95% CI 50.1–76.4%), respectively, p = 0.0008. The patients who achieved CR + uCR after having received first-line therapy had better outcomes compared to patients in PR. The 5- year overall survival rate in uCR + CR patients treated with R-CHEMO + RM1 and PR patients treated with R-CHEMO + RM1 was 90.6% and 68.3%, respectively, p = 0.0019. Rituximab maintenance treatment in patients 65 years and older yielded improved survival rates in a real world clinical setting. The R-CHOP regimen seems to be a more effective induction agent than R-CVP but the outcome of less intensively treated patients with R-CVP + RM is also acceptable. The achievement of uCR + CR after first-line therapy is associated with a better outcome.

1. Introduction

Follicular lymphoma (FL) is considered to be an incurable disease, but most patients can survive for many years. [1] The indolent course of the disease is typically characterized by an initial response to the induction of immunochemotherapy but the disease typically relapses within several years. Many clinical trials have shown the clinical benefits of the addition of rituximab to the first-line chemotherapy regimen in terms of a better progression free survival (PFS) and overall survival rate (OS) [2,3]. Presently, combined chemotherapy with rituximab (R-CHEMO) is regarded as a state of the art in first-line treatment of follicular lymphoma. Rituximab maintenance therapy (RM) is

* Corresponding author.
E-mail address: david.belada@seznam.cz (D. Belada).

https://doi.org/10.1016/j.leukres.2018.08.019
Received 20 June 2018; Received in revised form 27 August 2018; Accepted 29 August 2018
Available online 31 August 2018
0145-2126/ © 2018 Elsevier Ltd. All rights reserved.

implemented in patients who have achieved at least partial remission after the implementation of R-CHEMO based on the positive results of the PRIMA study [4]. The median PFS in the cohort of patients treated with immunochemotherapy (R-CHOP, R-CVP or R-FCM) followed by RM treatment at a dose of 375 mg/m [2] that was given every 2 months for a duration of 2 years is 10.5 years but so far, no survival benefit has been observed this study [5]. In the ECOG-ACRIN (E1496) study, similar results were seen with an improved PFS but no overall survival benefit after the R-CVP with RM were given in four doses that were spread six months apart for a period of two years [6]. However, there are only a few clinical trials designed especially for elderly patients. Moreover, elderly patients are often excluded from clinical trials due to comorbidities or impaired organ functions and they often refuse to participate in clinical trials.

The optimal rituximab dosing schedule is still unclear as there are many dosing schedules with no direct comparison [7–9]. Recently published data about the comparable efficacy of RM given every 3 months compared with a schedule of every 2 months after induction therapy with R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone) or BR (bendamustine + rituximab) were presented [10,11]. The results from a few retrospective analysis has shown not only a PFS benefit but also an OS advantage in favour of RM, but this data is limited only to patients who were treated initially with R-CHOP. More recently, RM has been shown to have a PFS benefit after an induction treatment with BR [12].

Follicular lymphoma is typically a disease of older patients, with the median age of diagnosis at around 60 years. Age is an independent negative prognostic factor in lymphoma patients [13]. Elderly patients with lymphoma suffer from therapy-related toxicities more frequently than younger patients. Standard induction therapy with R-CHOP cannot be used in all elderly patients due to comorbidites precluding the use of anthracyclines. The fludarabine-based regimen given to elderly patients with comorbidities (expecially impaired renal functions) is more likely to be associated with significant myelotoxicity. Bendamustine-based regimens are effective as first-line treatment of FL patients and are widely used in many countries but there is some evidence concerning higher toxicity from a recently published GALLIUM study [14]. Taking into account the indolent course of the disease, R-CHOP and R-CVP (rituximab, vincristine, prednisone) are the most commonly used first-line regimens in elderly patients with FL. In patients 80 years of age or over, R-CVP is a usually preferred regimen. Age-related comorbidities, such as cardiac disease, chronic obstructive pulmonary disease, impaired renal or hepatic functions are indications for reducing the dose of chemotherapeutics. The administration of chemotherapy in elderly patients is often associated with the risk of myelosupression due to a reduced bone marrow reserve and leads to the prolonged recovery of the blood count and a necessity to reduce the doses of chemotherapy, delaying the treatment schedule or a reduction of the number of cycles of therapy. Infectious complications are more likely to be seen in elderly patients during RM treatment due to B-cell depletion and hypogammaglobulinemia [15]. In the case of recurrent infections, the dosing intervals of rituximab needs to be prolonged. In the event of severe infectious complications, RM has to be interrupted for a longer period until the infection is confirmed to be resolved or definetely stopped. The elderly patients face various problems in complying with treatment such as challenges associated with travelling to the facility, not having the necessary assisstance at home, lack of motivation to carry on with the treatment etc. All of this factors can negatively affect the treatment outcome. In this situation, the use of modern methods, such as the Comprehensive Geriatric Assessment (CGA) is important to categorize the patients as being fit, unfit and frail [16]. The intensity of the therapy given is adjusted based on the fitnes of the patient. On the other hand, the meaningful progress in supportive care has been achieved in recent years and it has enabled the administration of immunochemotherapy even in very old patients.

The aim of our analysis was to evaluate the impact of RM treatment in a cohort of elderly patients ≥ 65 years of age with newly diagnosed FL in a real world setting and to assess the effects of R-CHEMO treatment (R-CHOP vs. R-CVP). Finally, we evaluated the significance of the quality of the response to the first-line treatment in the outcome of patients treated with RM. This prospective study was done using data from the Czech National Lymphoma Registry (NiHIL) - GovTrial Number NCT03199066 – a part of the NiHIL project.

2. Patients and methods

2.1. Study design

This study evaluated the efficacy of RM treatment in elderly patients ≥ 65 years with newly diagnosed FL. Patients were treated in the lymphoma centres throughout the Czech Republic between May 2003 and December 2014. All patients signed informed consent forms before the data was entered into the database. The review of all histopathology reports was carried out centrally, with incomplete or inconclusive reports not being included in the database. Data collected from the NiHIL was collected, updated and followed up annually. All enrolled patients are followed until progression, death or loss of a follow-up.

2.2. Eligibility criteria

A total of 1290 patients with newly diagnosed FL treated initially with R-CHEMO were registered in the NiHIL between 2003 – 2014. Patients with histological transformations due to the aggressive lymphoma before the start of R-CHEMO therapy were excluded. Patients on a watch and wait strategy were included in this analysis at the time of symptomatic disease progression thus fulfilling the GELF criteria for the start of R-CHEMO treatment. Only patients who responded to the initial R-CHEMO with CR or PR and were candicates for RM, were included and analyzed in this project. Selecting only elderly patients ≥ 65 years at the time of treatment initiation, we identified 232 consecutive patients from NiHIL with newly diagnosed and histologically confirmed FL, grades 1-3 A, who were indicated to begin R-CHEMO therapy. Patients who presented with further progression of follicular lymphoma within four months after the end of induction treatment were not enrolled in the study in order to avoid discriminating the group under observation due to early progression. The initial staging of follicular lymphoma is based on the medical history of the patient, the physical exam findings, results of various imaging tests (CT and PET scans of the head, neck, chest and abdomen plus echocardiography), unilateral bone marrow biopsy plus hematology, biochemical and virology tests.

2.3. Treatment

All patients need to be treated initially with R-CHEMO. The most commonly used first-line regimen was R-CHOP (n = 160) and R-CVP (n = 57). Other regimens have been used only rarely: 5x FCR (fludarabine, cyclophosphamide, rituximab), 3x FR (fludarabine, rituximab), 3x BR, 3x COPP (cyclophosphamide, vincristine, procarbazine, prednisone), 1x chlorambucil monotherapy. Rituximab biosimilars were not used in this study as they were not available during this time period in the Czech Republic. The final assessment of induction therapy was confirmed by CT or PET/CT scans. Since 2004, RM has been utilized as part of the first-line treatment of patients with FL in Czech Republic. The process of introducing RM into routine clinical practice in Czech Republic was generally slow because of the financial issues and varied from center to center, so the proportion of patients treated with RM (RM1) has been gradually increasing over time. Other patients were only observed without rituximab maintenance therapy (RM0) and this cohort served as a control arm. Both of the cohorts are not contemporary. At the initiation of the study, a higher proportion of patients were on observation and at the same time, a lower proportion of patients were started with RM treatment. As time progressed, the number

Download English Version:

https://daneshyari.com/en/article/10143099

Download Persian Version:

https://daneshyari.com/article/10143099

Daneshyari.com