EMBT LWP 2017-R-05 Research Protocol: Outcomes of patients treated with Ibrutinib post autologous stem cell transplant for mantle cell lymphoma.
A retrospective analysis of the LWP-EBMT registry.

Principle investigators

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Introduction

The current standard of care for fit patients with newly diagnosed, symptomatic Mantle Cell Lymphoma (MCL) is induction chemotherapy incorporating high dose Cytarabine and Rituximab followed by a consolidation autologous stem cell transplant (ASCT)[1,2]. This treatment approach is not curative and when patients relapse a variety of second line strategies may be employed. Ibrutinib, the first in class Bruton's Tyrosine Kinase (BTK) inhibitor has demonstrated promising activity in relapsed MCL[(3,4,5,6)]. However, there is little published data regarding the response to and efficacy of Ibrutinib in patients failing a first line ASCT.

In the pivotal phase 2 trial, 111 patients with a median age of 68 were treated with Ibrutinib for relapsed or refractory Mantle Cell Lymphoma[3,4]. With a median follow up of 26.7 months, the overall response rate (ORR) was 67% with a complete response (CR) rate of 23%. Median duration of response was 17.5 months and median overall survival (OS) was 22.5 months. These data included unfit elderly patients and did not analyse separately those with a prior autologous SCT (ASCT). A recent publication of 'real world' data of 97 patients treated with Ibrutinib for relapsed and refractory MCL identified 38 patients who had relapsed post ASCT[5]. 25 (66%) of those responded to Ibrutinib, with a median duration of response of 14 months. Prior ASCT was not associated with Ibrutinib response.

A randomised open label study compared Ibrutinib with Temsirolimus for patients with relapse or refractory MCL (n=280)[6]. ORR was significantly better for Ibrutinib (72% vs. 40%, $p<0.0001$) with a significant progression free survival (PFS) benefit (14.6 months vs. 6.2 months). Ibrutinib was better tolerated than Temsirolimus, with significantly fewer patients discontinuing Ibrutinib due to adverse events (6% vs. 26%). The study does not describe how many of these patients had a prior ASCT.

For patients who respond to Ibrutinib, allogeneic SCT (alloSCT) can be considered, though there is little evidence to guide such decisions. A cohort of 9 patients with relapsed MCL, 8 of whom had had a prior autologous stem cell transplant, received Ibrutinib followed by allogeneic SCT with a 1 year progression free survival of 75% and OS of 75% and no adverse impact on engraftment, graft-vs-host disease or non-relapse mortality[7].

Patients who discontinue Ibrutinib due to disease progression or toxicities appear to have poor outcomes. In a cohort of 42 patients, those with progressive disease after discontinuing Ibrutinib had low response rates to salvage therapy, with CR rates of 19% and a median overall survival of 8.4 months (with a median follow up of 10.7 months)[8].

Therefore, there remain unanswered questions regarding the efficacy of Ibrutinib in patients with MCL relapsing after induction chemotherapy and ASCT. This study aims to identify the efficacy of Ibrutinib in this setting whether used as a stand alone therapy or as a bridge to an allogeneic SCT.

Objective

To evaluate the outcomes of patients with MCL who receive Ibrutinib for relapse following the current standard first line therapy in fit patients (Rituximab containing induction regimes and ASCT in first response).

Study Design

Retrospective EBMT registry based analysis.

Primary endpoints

In patients with relapsed MCL following rituximab containing induction therapy and ASCT in first response (CR/PR 1):

- Response to treatment with Ibrutinib, i.e. achieving CR or PR at any time
- Duration of response to Ibrutinib treatment (defined as time spent in CR or PR)

Secondary endpoints

- Outcome at last follow up:
    - Proportion of patients remaining on Ibrutinib
    - Proportion of patients in whom Ibrutinib was stopped due to progression
    - Proportion of patients in whom Ibrutinib was stopped due to toxicity
    - Proportion of patients receiving any subsequent therapy for progressive disease after stopping Ibrutinib
- OS from time of relapse after ASCT to death of any cause

- Proportion of patients who received an alloSCT following Ibrutinib treatment
- Outcome of patients who undergo an allogeneic SCT after Ibrutinib (NRM, incidence of relapse (IR), PFS, OS, acute and chronic GvHD)

Inclusion Criteria

- Age≥18 years at diagnosis
- Histological diagnosis of mantle cell lymphoma (MCL)
- First Autologous stem cell transplant
- Induction immunochemotherapy with a Rituximab containing regimen
- Achieved a CR or PR after 1 or 2 lines of induction treatment
- ASCT in first response (CR/PR 1)
- Relapse on or after 1st October 2014 (date of European licence grant for Ibrutinib) and before January 2017

Exclusion criteria

- Not treated with Ibrutinib for relapse after ASCT

Data required

1. Patient demographics
    a. Age (Med A)
    b. Sex (Med A)
    c. Date of diagnosis (Med A)
    d. Disease stage at diagnosis (Med B)
    e. MIPI score and Ki67 (Med A if after Dec 2015, Med C if before Dec 2015)
2. Induction chemotherapy
    a. Regime(s) received (Med B)
    b. Number of lines to achieve first response (Med B)

3. Autologous SCT
    a. Date of transplant (Med A)
    b. Disease status at transplant (Med A)
    c. Performance status at transplant (Med B)
    d. Preparative regime utilised for ASCT (TBI yes/no and BEAM/LACE/BEAC/CyTBI/CBV/Other conditioning) (Med A)
    e. Best response after ASCT (Med A)
4. Relapse/progression after ASCT
    a. Date of relapse/progression (Med A)
5. Ibrutinib therapy at relapse
    a. Date of start (Med C)
    b. Stop date/ongoing therapy (Med C)
    c. Maximal response achieved at any time during Ibrutinib therapy (Med C)
    d. Duration of response (time in CR or PR) (Med C)
    e. Date of relapse/progression whilst on Ibrutinib (Med C)
    f. Reason for stopping Ibrutinib (relapse/toxicity/allogeneic SCT) (Med C)
6. Outcomes
    a. Survival status (Med B)
    b. Date of death (Med B)
    c. Cause of death (Med B)
    d. If applicable – did the patient receive subsequent therapy after stopping Ibrutinib (yes/no) (Med C)
    e. Whether patient proceeded to allogeneic SCT (yes/no) (Med C)
    f. If applicable – characteristics and outcomes of allogeneic SCT (Med A for allogeneic SCT)
        i. Date of allogeneic SCT

ii. Donor type (matched sibling, matched unrelated, mismatched unrelated, mismatched family, cord)

iii. Myelo-ablative or reduced intensity conditioning

iv. Date of neutrophil and platelet engraftment

v. GvHD

    1. Acute GvHD and grade if present

    2. Chronic GvHD and grade if present

vi. NRM – date and cause of death

Feasibility

A preliminary search of the EBMT registry identified 509 patients who have relapsed after 1/10/14 following autologous SCT in CR1/PR1 for MCL, information on treatment post relapse is available in 107 patients and Ibrutinib post SCT is registered in 47. Based on these numbers, assuming 50% of all (N=509) patients did receive Ibrutinib, 255 patients are expected to meet inclusion criteria. Assuming a 40% response rate, around 100 patients would be included in the final analysis.

Statistical analysis

The response rate will be estimated and factors associated with response will be investigated using logistic regression.

Probabilities of OS will be calculated using Kaplan-Meier test. The risk of acute and chronic GVHD after alloSCT will be calculated using cumulative incidence estimates to take into account the competing risk structure. Multivariate analyses will be performed using Cox proportional hazards regression using a stepwise conditional backward method.

Central review of written histology reports

Will not be performed for this purpose of the study

Timeline

- Protocol approved by EMBT LWP and assigned 'medium' priority – 20th Sept 2017
- Invitation to centres Feb 2018
- Deadline for data retrieval – June 2018
- Abstract to be sent to – ASH 2018 (abstract deadline August 2018)
- Manuscript for publication – Winter 2018

Participating centres

All centres with appropriate Med A and follow up data on eligible patients in the data base and willing to submit additional Med C data.

Administration and budget

Study coordinator: Hervé Finel

Statistician Ariane Boumendil

LWP chairperson: Silvia Montoto

Envisaged staff time: TBC

Budget: LWP variable budget

References

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