SYNOPSIS
Observational study on the use of B cell receptor kinase inhibitors and BCL2 antagonists prior to allogeneic hematopoietic stem cell transplantation for B cell malignancies: A joint project of the EBMT Lymphoma and Chronic Malignancy Working Parties

EBMT Study code: LWP 2013-N-02 / CMWP 44204425

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BACKGROUND AND RATIONALE
Allogeneic hematopoietic stem cell transplantation (HSCT) is an accepted treatment option for fit and otherwise eligible patients with relapsed and refractory B cell lymphomas or high-risk chronic lymphocytic leukemia (CLL) ¹.

However, the established treatment algorithms of B cell lymphoma and CLL are currently questioned by the introduction of novel classes of drugs which are characterized by modes of action that are fundamentally different from traditional cytotoxic agents and antibodies ²-⁴. The best developed of these appear to be compounds inhibiting kinases downstream of the B cell receptor, such as ibrutinib and idelalisib (B cell receptor tyrosine kinase inhibitors, BCRi), and selective BCL-2 antagonists (BCL2a), such as ABT-199 ⁵-⁷. Although the available information is still very limited and lacks sound follow-up, preliminary observations strongly suggest that these agents have the potential to fundamentally change the standard treatment of B cell lymphoma and CLL including the role of HSCT in the near future.

As of today, however, actual mid- and long-term efficacy and toxicity, optimum mode of use (combination partners, treatment line, sequence), timelines of availability and future impact on treatment standards of the new drugs are largely unclear. Although individual patients treated in the BCRi/BCL2a trials to date have discontinued study treatment in favour of proceeding to HSCT ² ⁸, there is virtually no information if exposure to one or more of the new drugs could impact on the outcome of subsequent allotransplantation. It is also unknown how effective HSCT can be in patients with lymphoma/CLL relapse/ progression under BCRi/BCL2a.

The purpose of the present study is to provide information on the potential risks and benefits of previous BTKi/BH3m exposure on subsequent allogeneic HSCT as performed previously for other targeting drugs ⁹.

ELIGIBILITY
Inclusion Criteria:
- First allogeneic HSCT
- Diagnosis of MCL, CLL, FL, WM or DLBCL
- Age over 18 years at transplant
- Allografted 2013-March 2015
- Donor SIB or well or partially matched unrelated
- Any conditioning regimen
- Documented pre-transplant exposure to BCRi/BCL2a, such as
  - Ibrutinib
  - CC-292
  - ONO-4059
  - Idelalisib
  - IPI-145
  - ABT199

**STUDY TYPE**
Observational registry-based analysis.

**OBJECTIVES**
To assess safety and efficacy of HSCT after previous exposure to BCRi/BCL2a

**PRIMARY END-POINT**
- Non-Relapse mortality (NRM) at 12 months: Assessment of time from HSCT to death without previous disease relapse or progression in patients who had BCRi/BCL2a exposure prior to HSCT (taking into account relapse as competing risk)

**SECONDARY END-POINTS**
- Time to engraftment: Assessment of days from HSCT to ANC >0.5/nl and of days from HSCT to platelets >20/nl
- Incidence of grade 2-4 and 3-4 acute GVHD
- Disease relapse or progression incidence (RI): Assessment of time from HSCT to relapse or progression in (taking into account NRM as competing risk)
- Progression-free survival (PFS): Assessment of time from HSCT to relapse, progression, or death from any cause
- Overall survival (OS): Assessment of time from HSCT to death from any cause
- Prognostic factor analyses considering type of novel drug, underlying disease, remission status at HSCT and other potential confounders.

**DATA ITEMS TO BE COLLECTED**
will include the following (Med A / B):

**Baseline Characteristics**
- Age (A)
- Sex (A)
- Diagnosis (A)
- B symptoms (B)

Lymphoma only:
- Stage Ann Arbor (B)
- BM involvement (B)
- CNS involvement (B)
- Other sites of extra nodal disease (B)
- Bulky mass and size (B)
- LDH (B)

CLL only:
- Binet Stage (B)
- 17p- or TP53 abnormality (B)
- 11q- (B)

**Treatment Pre-HSCT**
- Treatment details prior to HSCT (for each therapeutic regimen: type, date started, date stopped, response (B)
- Type of novel drug and date, dose and duration of administration (C – to be reported on the registration form)

**HSCT Details**
- Day of transplant (A)
- Status at transplant (A/B)
- Performance status (A)
- HCT-CI (A/B)
- Conditioning regimen (A)
- Donor type and match (A)
- Cell source (B-Allograft)

**Toxicity**
- Time to neutrophil recovery >0.5 (A)
- Time to platelet recovery >20 (A)
- Acute GVHD (A)
- Chronic GVHD (A/B)

**Outcome**
- Status at last follow-up (A)
- Date of last follow-up (A)
- Day +100 response (A)
- Relapse – y/n (A)
- Date of relapse, if applicable (A)
- Cause of death, if applicable (A)
- Date of death, if applicable (A)
- Secondary malignancy (A)
- If re-treatment after HSCT with BCRi/BCL2a: type of novel drug and date of administration (B); additional cellular therapy (A); additional immunotherapy / chemotherapy (B)

**STATISTICAL ANALYSIS**
Descriptive survival analysis as described under Endpoints

Univariate and multivariate analyses for studying association of patient and transplant variables with primary and secondary survival endpoints
- Comparison between groups using t-tests or Mann-Whitney U test as indicated
- Survival curves for OS and PFS will be estimated by the Kaplan Meier method
- Univariate assessment of type of novel drug, underlying disease, and other prognostic factors associated with OS and PFS will use the log-rank test.

- Cumulative incidence curves taking into account the competing risk structure of the event will be estimated for NRM, and RI.

- Univariate assessment of type of novel drug, underlying disease, and other prognostic factors associated with NRM and RI will use Gray's test.

- Prognostic factors to be considered: Conditioning regimen; age, sex, interval diagnosis-SCT, remission status at SCT (CR>1/PR>1 vs REL, REF, PD), pretreatment lines, 17p-/TP53 status at HSCT.

- Multivariate assessment of the impact of prognostic factors on OS and PFS will use Cox regression models for adjustment for the other prognostic factors.

- Multivariate assessment of the impact of prognostic factors on NRM and RI will use Fine & Gray regression model (consideration of competing risk structure) for adjustment for the other prognostic factors.

- The variables of the toxicity endpoints will undergo descriptive statistics and will be compared by non-parametric tests where appropriate.

**SAMPLE SIZE**

Accrual will be stopped as soon as 30 eligible patients with CLL or MCL exposed to ibrutinib are potentially evaluable for primary endpoint (irrespective of the overall number of accruals for other diagnoses and drugs).

**DATA COLLECTION**

Data to be collected from Med A and Med B forms plus individual Med C levels items to be requested from the centres.

**CENTRAL REVIEW OF WRITTEN HISTOLOGY REPORTS**

Will not be performed for the purposes of this study.

**TIME FRAME / MILESTONES**

Registration of patients completed: March 31, 2015.
Deadline for data retrieval: May 31, 2016
Data analysis complete: July 31, 2016 for an ASH Meeting Abstract Submission.

**PARTICIPATING CENTRES**

All centers with appropriate baseline and follow-up data on eligible patients in the database.

**ADMINISTRATION AND BUDGET**

Study Coordinators: Hervé Finel for LWP / Anja van Biezen for CMWP. Lymphoma patients will be registered with the Paris office; CLL patients will be registered with the Leiden office.

Statistician: Ariane Boumendil
WP chairpersons: Peter Dreger / Nicolaus Kröger

Envisaged staff time: 150h study coordinator, 75h statistician, 60h week WP chairs / EBMT PIs (WP chairperson / PI time granted by EBMT)

Budget: 30,000 EUR (incl. publication and administrative costs – to be secured)

REFERENCES


