CLSG-MCL-01: PROTOCOL

Study Design:

A prospective, mutlicenter, observational study considered for patients meeting these basic criteria:
-a confirmed diagnosis of MCL (hematopathologic examination in the reference center, with evidence of cyclin D1, or translocation t(11; 14))

Population:
-inability to undergo intensive treatment including high-dose therapy with autologous stem cells transplantation
- treatment according to standard protocol.(R-CHOP/R-AraC)....
-ability to be treated with R-CHOP-like chemotherapy regimen.

The study enrolled patients who were treated according to standard protocol used in the hematologic department on a proposal made by the attending physician and the patient's consent. For the purposes of this observational study the patient signed patient informed consent form with participation in the study and processing of data.

Treatment protocol:

Scheme: alternating cycles of R(ituximab)-CHOP and R-HDAC (high-dose araC): R-CHOP/R-HDAC/R-CHOP/R-HDAC/R-CHOP/R-HDAC
Doses: R-CHOP - standard immunochemotherapy - Rituximab (R) - 375mg/m2 day 1, Cyclophosphamide (C) - 750mg/m2 day 1, doxorubicin (H) - 50mg/m2 day 1, vincristine (O) - 2mg Day 1 , Prednisone (P) - 100 mg / d days 1-5).
R-AraC - standard immunochemotherapy in a dose of 1g/m2 or 2g/m2 once daily for two days.
Supportive therapy: not specified, based on the particular center practise, the use of G-CSF praphylaxis according to EORTC recommendations.
After induction treatment rituximab maintenance therapy or observation based on standards of each center could be given. Three scenarios were expected - 1. no maintenance therapy was given to the patient; 2. no maintenance therapy was given to the patient, but when molecular positivity reappeared (testing provided in local laboratories) rituximab was administered; 3. maintenance rituximab was administered once in 3 months at a dose of 375 mg/m2.

Diagnostic procedures:

Examination: according to standard recommendations: before initiation of therapy, after 3 cycles and after completion of induction (i.e. after 6 cycles). Restaging procedures in the follow-up phase –based on particular center practise.
Standard medical examinations: - clinical, CT scans, analysis of the bone marrow and peripheral blood including flow cytometry, cytogenetics (possibly FISH), and PET scans if available.
CT scans were done before treatment, after 3 cycles of therapy, and after 6 cycles of therapy.
PET scans were implemented in all patients after 6 cycles. If available at the center, PET scans were also done before therapy initiation, and after 3 cycles of therapy.
Evaluation was done visually according to the Deauville five-point score.
Bone marrow: trephine biopsy was performed before treatment and at the end of treatment after 6 cycles in case of initial bone marrow infiltration with lymphoma.
The only study related examination: flow cytometry and molecular determination of MRD - performed in a central laboratory authorized by the European Network of MRD laboratories (EuroMRD): CLIP (Childhood Leukemia Investigation Prague) Laboratory at the University Hospital Motol Prague (http://clip.lf2.cuni.cz/en/).

Data analysis:

-central registration in the Data Center of CLSG
-paper CRF forms fillled for each patient during the study
-Clinical data are collected centrally in CLSG Data Center

-MRD data are collected in CLIP database and transfered to CLSG Data Center to be matched with clinical data Patients, who met the inclusion criteria, and who had signed the informed consent, were centrally registered in the data center of the Czech Lymphoma Study Group (CLSG). For each patient the case report form (CRF) was filled in at the given center, the results from central MRD assessment were filled in at the central CLIP laboratory.

Cohort size and statistical analysis:

This is a prospective observational study with a cohort size of 73 patients recruited since 9.7.2011 until 17.8.2015. By 15.12.2016 the median follow-up of the living patients was 3.65 years. The statistical analysis will be based on parametric and nonparametric tests, survival analysis will be calculated using the Kaplan-Meier model, Cox's model will be used to test the prognostic significance in multivariate analysis. CLSG database will be used for comparison with historical controls, where it is now processed more than 250 patients with MCL with supplementing retrospective data (D Salek, ASH 2009).

Cooperation:

The study was based on collaboration between hematologic centers in the Czech Republic, which has been ongoing for many years. At the same time it uses (especially in data acquisition and information exchange) cooperation within the European Mantle Cell Lymphoma Network (a joint project of the European lymphoma groups). As a part of the ongoing standardization of MRD detection in lymphomas we cooperate with all participating centers of the EuroMRD group (Amsterdam, Creteil, Grenoble, Kiel, Lisbon, Rotterdam, Salamanca, Torino, Turku). Twice a year we participate in quality control and joint regular meetings. We are involved in the standardization of detection of mature B-lymphocyte malignancies using multicolor flow cytometry within the framework of the group EuroFlow.