LymphomaHub

MCL

8.5-year follow-up of MCL2 and MCL3 trials: post-ASCT pre-emptive rituximab for MRD relapse resulted in temporary molecular remissions in patients with Mantle Cell Lymphoma

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Recently in Biology of Blood and Marrow Transplantation, Arne Kolstad from Oslo University Hospital, Radiumhospitalet, Oslo, Norway, and colleagues published an analysis of two Nordic Lymphoma Studies (MCL2 and MCL3) after a median follow-up of 8.5 years.

The main aims of this analysis were to monitor MRD in the bone marrow of MCL patients to predict clinical relapse and guide pre-emptive rituximab therapy. In the two prospective Nordic Lymphoma Group trials, 183 had completed ASCT and had an MRD marker observed by qRT-PCR (Bcl-1 or IgH rearrangement) and so were included in the current analysis (median age, 57; range, 28–65).

Patients in the MCL2 trial were administered up to 6 cycles of alternating maxi-CHOP-R and R-Ara-C, and then underwent ASCT. In MCL3, the induction regimen stayed the same but responding patients not in CR before ASCT were administered yttrium-90 ibritumomab tiuxetan.

Key Highlights:

Outcomes relative to MRD status pre- and post-ASCT

- MRD-positive pre-ASCT = 54 pts (42%)
  - PFS and OS were significantly shorter in MRD-positive compared to MRD-negative pts ($P = 0.0002$; $P = 0.009$)
- MRD-positive in first sample post-ASCT = 23 pts (13%)
  - Median PFS in MRD-positive and MRD-negative pts was 20 months *vs* 142 months, respectively ($P < 0.0001$)
  - Median OS in MRD-negative and MRD-positive pts was not reached *vs* 35 months, respectively ($P < 0.0001$); 10-yr OS in MRD-negative pts = 75%

Risk of clinical relapse after molecular relapse

- For all 183 pts, median time from ASCT to first molecular relapse = 55 months
- MRD-negative in all analyses post-ASCT = 86/183 pts (47%); 63 (73%) are still alive and in clinical remission; 19 (22%) relapsed clinically; 4 died from other causes

- MRD-positivity at any time post-ASCT = 97/183 pts (53%); 64 (66%) also relapsed clinically, in 27 of these clinical relapsed occurred simultaneously or within 3 months of molecular relapse and most did not receive pre-emptive rituximab

Outcomes after pre-emptive rituximab therapy

- Pre-emptive rituximab administered to 58 pts
- Continuous remission = 28 pts (48%); clinical relapse = 30 pts (52%)
- Twenty-five pts were administered rituximab for molecular relapse on multiple occasions
- Of rituximab treatments with subsequent samples, 80/92 (87%) led to MRD-negativity
- Among all rituximab-treated pts who became MRD-negative, 34 (69%) became MRD-positive again in a subsequent sample, indicating rituximab's effect was temporary

Predictors of molecular relapse

- Pts allocated as high risk by the MIPI and MIPI-C had significantly shorter time to molecular progression (25 months and 19 months) *vs* lower-risk groups
- On multivariate analysis, significant predictors of molecular relapse were:
  - MIPI high risk at diagnosis (HR, 1.908; 95% CI, 1.368–2.661; $P = 0.0001$)
  - Detection of MRD before ASCT (HR, 2.465; 95% CI, 1.486–4.090; $P = 0.0005$)

The authors stated that the results of their large prospective study stresses the importance of inducing molecular remission in MCL and the continuous pattern of molecular relapses observed supports the present opinion that MCL in incurable.

They concluded that treatment with pre-emptive rituximab for MRD relapse resulted in temporary molecular remissions; the authors suggest that maintenance with rituximab is a potential strategy for keeping "patients in stable molecular remission and delay clinical relapse."

Lastly, the authors noted that the poor prognosis of patients who were MRD-positive in their first sample post-ASCT is of great concern and "novel strategies are urgently needed."

Abstract:

The main objectives of the present study were to monitor minimal residual disease (MRD) in the bone marrow of patients with mantle cell lymphoma (MCL) to predict clinical relapse and guide preemptive treatment with rituximab. Among the patients enrolled in 2 prospective trials by the Nordic Lymphoma Group, 183 who had completed autologous stem cell transplantation (ASCT) and in whom an MRD marker had been obtained were included in our analysis. Fresh samples of bone marrow were analyzed for MRD by a combined standard nested and quantitative real-time PCR assay for Bcl-1/immunoglobulin heavy chain gene (IgH) and clonal IgH rearrangements. Significantly shorter progression-free survival (PFS) and overall survival (OS) was demonstrated for patients who were MRD positive pre-ASCT (54 patients) or in the first

analysis post-ASCT (23 patients). The median PFS was only 20 months in those who were MRD-positive in the first sample post-ASCT, compared with 142 months in the MRD-negative group (P < .0001). OS was 75% at 10 years and median not reached in the MRD-negative group, compared with only 35 months in the MRD-positive group (P < .0001). Of the 86 patients (47%) who remained in continuous molecular remission, 73% were still in clinical remission after 10 years. For all patients, the median time from ASCT to first molecular relapse was 55 months, with a continuous occurrence of late molecular relapses. Fifty-eight patients who experienced MRD relapse received rituximab as preemptive treatment on 1 or more occasions, and in this group, the median time from first molecular relapse to clinical relapse was 55 months. In most cases, rituximab converted patients to MRD negativity (87%), but many patients became MRD-positive again later during follow-up (69%). By multivariate analysis, high-risk Mantle Cell Lymphoma International Prognostic Index score and positive MRD status pre-ASCT predicted early molecular relapse. In conclusion, preemptive rituximab treatment converts patients to MRD negativity and likely postpones clinical relapse. Molecular monitoring offers an opportunity to select some patients for therapeutic intervention and to avoid unnecessary treatment in others. MRD-positive patients in the first analysis post-ASCT have a dismal prognosis and thus are in need of novel strategies.

Reference:

1. Kolstad A. *et al.* Molecular Monitoring after Autologous Stem Cell Transplantation and Preemptive Rituximab Treatment of Molecular Relapse; Results from the Nordic Mantle Cell Lymphoma Studies (MCL2 and MCL3) with Median Follow-Up of 8.5 Years. Biol Blood Marrow Transplant. 2017 Mar;23(3):428-435. DOI: 10.1016/j.bbmt.2016.12.634. Epub 2016 Dec 27.

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