High dose cytarabine with rituximab is not enough in first-line treatment of mantle cell lymphoma with high proliferation: early closure of the Nordic Lymphoma Group Mantle Cell Lymphoma 5 trial

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To the Editor

Early closure of the Nordic Lymphoma Group MCL5 Trial: Rituximab and high-dose AraC in high-risk Mantle cell lymphoma.

The Nordic Lymphoma Group Mantle Cell Lymphoma 5 trial "MaRit" was launched in 2011 (EudraCT EU 2011-001557-85) aimed to improve the outcome of younger MCL patients with high MIPI or MIPI-B scores. The induction treatment consisted of six cycles of high-dose AraC, rituximab and dexamethasone (Figure 1). Responders to cycle 5, received the sixth cycle for stem cell mobilization, followed by high-dose chemotherapy with BEAM and stem cell reinfusion. After the transplantation, patients in CR who were PCR-negative for their clonal IGHV rearrangement or bcl1, were to be followed with PCR of the bone marrow twice annually and to receive preemptive treatment with 4 wekly infusions of rituximab upon molecular relapse while still in clinical CR.

The background for this regimen was the experience gained from the Nordic MCL1-3 trials[1-4]. Compared to the results of the MCL1 trial using high-dose CHOP x 4 followed by BEAM and ASCT [1] the outcome was dramatically improved by the addition of rituximab and high-dose AraC, to a total of 6 induction cycles (R-maxi-CHOP alternating with R-AraC [2]. However, analysed according to the Mantle Cell Lymphoma International Prognostic Index (MIPI) [5] the outcome among high-risk patients was significantly inferior compared with low and intermediate risk [3], both in terms of response, response duration and of survival. Furthermore we identified high Ki-67 expression as the single most important prognostic factor[6].

With this in mind, and based on encouraging reports of induction with R-DHAP only [7], we designed the MCL5 as an early intensification in MIPI and MIPI-B high-risk (i.e. with high Ki-67 expression) patients, particularly aiming at increasing the exposure of these rapidly dividing tumours to the cell cycle active agent cytarabine, at the cost of the presumed inferior CHOP components. The European MCL Network has designed a similar trial for relapsed MCL with rituximab, high dose cytarabine and dexamethasone as backbone, randomizing the addition of bortezomib.

As the hematological and neurological toxicity might be higher in the MCL5 with the cumulated dose of 72 g/m^2 in 6 cycles and due to the excellent results in the good and intermediate risk groups of 70% 10 year survival in MCL2 and 3, the Nordic MCL5 was launched only for the MIPI-B poor risk.

Since the regimen was essentially untested, a safety and efficacy run-in was built in, stressing that any two of the following severe adverse events occurring among the first 10 patients should lead to a trial pause and reanalysis: Failure to respond, failure to harvest or unexpected severe adverse events, eg. neurotoxicity.

Five patients were included in the period January – June 2012 (Table 1). Only two responded after three cycles, while three did not respond. One patient (S001) with a bulky tumour involving the chest wall had no signs of efficacy at all after cycle two, and had to be taken off protocol for salvage treatment. The histology was not blastoid, but showed strong expression of p53 protein, suggesting TP53 mutation. Of note, all three non-responders subsequently responded to R-maxiCHOP.

Due to the stopping rule this trial was halted in December 31, 2012, and has now been definitively discontinued.

Recent controlled trials have confirmed that AraC containing regimens are superior to CHOP-like regimens[8]. In standard-risk MCL 1st-line Rituximab-AraC (R-HDA) also performed well[9]. Although doubts have been raised whether AraC containing regimens are able to control high-risk disease[10], Hermine et al also found a significant benefit of R-CHOP alternating with R-DHAP in the MIPI high-risk patients compared to R-CHOP alone.

Despite the low number of patients, the failures to R-HDA in 3 of 5 high-risk MCL patients and their subsequent salvage by R-maxiCHOP, send a signal not to be ignored, that single-agent high-dose AraC + rituximab is not the way forward in high-risk MCL. The combination of AraC with other agents such as the cisplatinum in DHAP or alternating with the CHOP components as in the Nordic and European regimens and the hyperCVAD-metothrexate-AraC may be important.

Besides, chemotherapy-resistant MCL may harbor genetic defects, e.g. TP53 mutations, rendering it resistant to any chemotherapy. New agents with distinct modes of action, such as ibrutinib may turn out to be a key to this problem.

Despite the low number of patients of this report, we feel compelled to inform the lymphoma community of these findings, which indicate that AraC, otherwise one of the most active agents in MCL, is not a universal solution in high-risk disease.

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Supplementary Material:

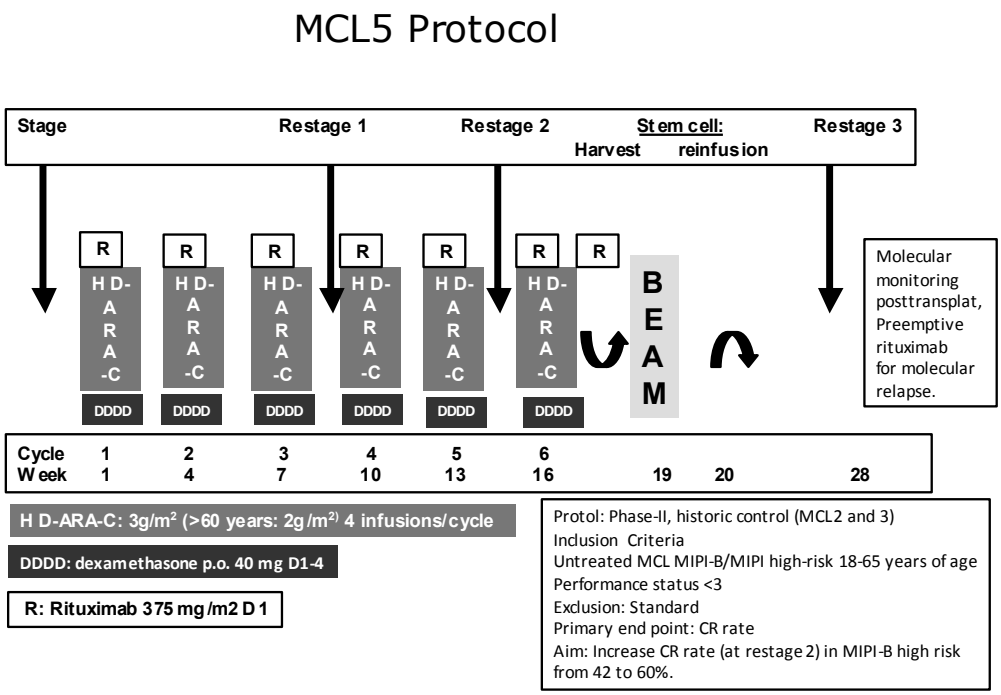
Details of the non-responding patients:

Patient N001 presented with widespread lymphadenopathy, splenomegaly , bone marrow involvement, MIPI low risk and Ki67 60%. He responded with a PR but a large abdominal nodal mass was unchanged after 4 courses of cytarabine. Biopsy showed viable lymphoma and treatment was changed to R-CHOP with a prompt response and he was continued to BEAM and ASCT.

Patient N002 presented with lymphadenopathy, a huge spleen and bone marrow involvement, MIPI intermediate risk and Ki67 50%. After four courses of cytarabine there was a PR in marrow and nodes but the huge spleen was unchanged. He was taken off study and treated with R-CHOP, responded and proceeded to BEAM and ASCT.

Patient S001 presented with a bulky (20x20cm) thoracic wall tumor involving soft tissue and adjacent nodes in the axilla and infraclavicular area but no other lymph nodes and no marrow involvement. MIPI was intermediate and Ki67 80%. After the first and second cytarabine course there was a regression but rapid re-growth. He was taken off protocol and received R-CHOP, responded well and proceeded to BEAM and ASCT.

Figure 1


MCL5 Protocol
Stage
Restage 1
Restage 2
Stem cell:
Harvest
reinfusion
Restage 3
R
H D-A RA-C
DDDD
BEAM
Molecular monitoring posttransplat, Preemptive rituximab for molecular relapse.
Cycle 1 2 3 4 5 6
Week 1 4 7 10 13 16 19 20 28
H D-ARA-C: 3g/m² (>60 years: 2g/m²) 4 infusions/cycle
DDDD: dexamethasone p.o. 40 mg D1-4
R: Rituximab 375 mg/m2 D 1
Protol: Phase-II, historic control (MCL2 and 3)
Inclusion Criteria
Untreated MCL MIPI-B/MIPI high-risk 18-65 years of age
Performance status <3
Exclusion: Standard
Primary end point: CR rate
Aim: Increase CR rate (at restage 2) in MIPI-B high risk from 42 to 60%.

First 5 Nordic Patients in MCL5

	WHO	nodes	spleen	bm	stage	LDH	Ki67	MIPI	MIPI-B		courses
N001	0	+	+	(+)	IVA	high	60%	low	high	fail	4
N002	1	+	++	+	IVB	high	50%	inter	high	fail	5
N003	0	+	+	+	IVA	high	50%	inter	high	CRu	6
S001	1	+	-	-	IVEA	high	80%	inter	high	fail	2
F001	1	+	+	+	IVB	nor	60%	low	high	PR	3+

References

1. Andersen NS, Pedersen L, Elonen E, et al. . Primary treatment with autologous stem cell transplantation in mantle cell lymphoma: outcome related to remission pretransplant. Eur J Haematol 2003;71:73-80.
2. Geisler CH, Kolstad A, Laurell A, et al. . Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693.
3. Geisler CH, Kolstad A, Laurell A, et al. . The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 2010;115:1530-1533.
4. Kolstad A, Laurell A, Jerkeman M, et al. . Nordic MCL3 Study: Zevalin Combined with High-Dose Chemotherapy Followed by Autologous Stem Cell Support As Late Intensification for Mantle Cell Lymphoma (MCL) Patients < 66 Years Not in CR After Induction Chemoimmunotherapy: No Benefit of Zevalin. . Blood (ASH Annual Meeting Abstracts) 2012;120:147.
5. Hoster E, Dreyling M, Klapper W, et al. . A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558-565.
6. Geisler CH, Kolstad A, Laurell A, et al. . Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol 2012;158:355-362.
7. Le Gouill S, Callanan M, Macintyre E, et al. . Clinical, Metabolic and Molecular Responses After 4 Courses of R-DHAP and After Autologous Stem Cell Transplantation for Untreated Mantle Cell Lymphoma Patients Included in the LyMa Trial, a Lysa Study

Blood (ASH Annual Meeting Abstracts) 2012;120:152.

8. Hermine O, Hoster E, Walewski J, et al. . Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (*MCL net*). . Blood (ASH Annual Meeting Abstracts) 2012;120:150.
9. Forbes A, Farrell K, McKay P, Bolam S, Rule S. High dose cytarabine with rituximab is an effective first-line therapy for mantle cell lymphoma and produces ample stem cell harvest yields after multiple chemotherapy cycles. Leuk Lymphoma 2013.
10. Budde LE, Guthrie KA, Till BG, et al. . Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. J Clin Oncol 2011;29:3023-3029.