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Eskelund, Christian W.; Kolstad, Arne; Jerkeman, Mats; Rätty, Riikka; Laurell, Anna; Eloranta, Sandra; Smedby, Karin E.; Husby, Simon; Pedersen, Lone B.; Andersen, Niels S.

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15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau

Christian W. Eskelund,¹ Arne Kolstad,² Mats Jerkeman,³ Riikka Rätty,⁴ Anna Laurell,⁵ Sandra Eloranta,⁶ Karin E. Smedby,⁶ Simon Husby,¹ Lone B. Pedersen,¹ Niels S. Andersen,¹ Mikael Eriksson,³ Eva Kimby,⁷ Hans Bentzen,⁸ Outi Kuittinen,⁹ Grete F. Lauritzen,² Herman Nilsson-Ehle,¹⁰ Elisabeth Ralfkiær,¹ Mats Ehinger,¹¹ Christer Sundström,¹² Jan Delabie,¹³ Marja-Liisa Karjalainen-Lindsberg,¹⁴ Christopher T. Workman,^{15,16} Christian Garde,^{15,16} Erkki Elonen,⁴ Peter Brown,¹ Kirsten Grønbaek¹ and Christian H. Geisler¹

¹Department of Haematology, Rigshospitalet, Copenhagen, Denmark, ²Department of Oncology, Oslo University Hospital, Oslo, Norway, ³Department of Oncology, Lund University Hospital, Lund, Sweden, ⁴Department of Haematology, Helsinki University Central Hospital, Helsinki, Finland, ⁵Department of Oncology, Uppsala University Hospital, Uppsala, ⁶Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institute, ⁷Department of Haematology, Karolinska Institute, Stockholm, Sweden, ⁸Department of Haematology, Aarhus University Hospital, Aarhus, Denmark, ⁹Department of Oncology and Radiotherapy, Oulu University Hospital, Oulu, Finland, ¹⁰Section of Haematology and Coagulation Medicine, Sahlgrenska University Hospital, Gothenburg, ¹¹Department of Pathology, Lund University Hospital, Lund, ¹²Department of Genetics and Pathology, Uppsala University Hospital, Uppsala, Sweden, ¹³Department of Pathology, Oslo University Hospital, Oslo, Norway, ¹⁴Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland, ¹⁵Department of Systems Biology, Technical University of Denmark, Lyngby, and ¹⁶Department of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Summary

In recent decades, the prognosis of Mantle Cell Lymphoma (MCL) has been significantly improved by intensified first-line regimens containing cytarabine, rituximab and consolidation with high-dose-therapy and autologous stem cell transplantation. One such strategy is the Nordic MCL2 regimen, developed by the Nordic Lymphoma Group. We here present the 15-year updated results of the Nordic MCL2 study after a median follow-up of 11.4 years: For all patients on an intent-to-treat basis, the median overall and progression-free survival was 12.7 and 8.5 years, respectively. The MCL International Prognostic Index (MIPI), biological MIPI, including Ki67 expression (MIPI-B) and the MIPI-B including miR-18b expression (MIPI-B-miR), in particular, significantly divided patients into distinct risk groups. Despite very long response durations of the low and intermediate risk groups, we observed a continuous pattern of relapse and the survival curves never reached a plateau. In conclusion, despite half of the patients being still alive and 40% in first remission after more than 12 years, we still see an excess disease-related mortality, even among patients experiencing long remissions. Even though we consider the Nordic regimen as a very good choice of regimen, we recommend inclusion in prospective studies to explore the benefit of novel agents in the frontline treatment of MCL.

Keywords: Mantle Cell Lymphoma, Non-Hodgkin Lymphoma, clinical trials, high dose therapy.

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Correspondence: Christian W. Eskelund,
Epigenome Laboratory, Department of
Haematology, Rigshospitalet, Building 2, 3rd
floor, Ole Maaløes Vej 5, 2200 Copenhagen N,
Denmark.
E-mail: christian.winther.eskelund.01@regionh.
dk

Traditionally, Mantle Cell Lymphoma (MCL) has been associated with a poor prognosis with a median overall survival of 3–5 years (Herrmann *et al*, 2009; Abrahamsson *et al*, 2014). However, during the last 10–15 years the treatment of MCL patients, especially younger cases, has been improved substantially by two developments: (i) intensified induction immunochemotherapy including cytarabine (Ara-C) and anti-CD20 antibodies, and (ii) consolidating high-dose therapy with autologous stem cell transplantation (ASCT) (Dreyling *et al*, 2005; Romaguera, 2005; Geisler *et al*, 2008; Hermine *et al*, 2012; Delarue *et al*, 2013). The value of ASCT has not yet been rigorously tested in the setting of intensive immunochemotherapy induction. Accordingly, the Nordic MCL2 trial reached a median 6-year progression-free survival (PFS) and overall survival (OS) of 66% and 70%, respectively (Geisler *et al*, 2008), and the updated version reported projected a 10-year PFS and OS of 43% and 58%, respectively (Geisler *et al*, 2012).

Mantle Cell Lymphoma remains a heterogeneous disease, necessitating prognostic models. The Mantle Cell Lymphoma International Prognostic Index (MIPI) and MIPI-B (biological MIPI including the Ki67 index), remain valid prognosticators also when tested in trials with long follow-up (Romaguera *et al*, 2010; Geisler *et al*, 2012; Hoster *et al*, 2014).

However, the search continues for new biomarkers to improve the risk stratification of patients, particularly those that can aid identification of patients with very aggressive disease. Such patients do not show satisfactory responses to standard therapy and therefore could benefit from alternative, novel treatment modalities (Oberley *et al*, 2013; Delfaularue *et al*, 2015; Husby *et al*, 2015).

In recent years, several novel biologically targeted agents have been introduced in MCL, mainly registered for use in the relapse setting (Wang *et al*, 2013; Robak *et al*, 2015; Ruan *et al*, 2015). Although these are in the process of moving up to frontline use, either alone or in combination with other therapy, the standard first line treatment of younger patients has remained largely unchanged since the introduction of the intensified protocols, such as the Nordic regimen (Geisler *et al*, 2008). Hence, we consider that this long-term update is still of clinical relevance for the continued follow-up and salvage treatment of these patients.

Here we present the updated results of the MCL2 trial, now reaching a median follow-up time of 11.4 years, with focus on relapse, survival and risk groups defined by MCL prognosticators. In the previous update of this cohort, with a median follow-up of 6.5 years, the median OS exceeded 10 years (Geisler *et al*, 2012). Now we show that relapses continue to occur even after 5 years, suggesting that the disease will not be eradicated by strategies that are considered standard for first line treatment of MCL today.

Material and methods

Patients

From 2000 to 2006 the Nordic Lymphoma Group (NLG) conducted a phase 2 trial, MCL2, for the initial treatment of MCL patients aged less than 66 years. Briefly, patients were newly diagnosed with stage II–IV MCL, all expressing cyclin-D1 (CCND1) or positive for t(11;14) according to the World Health Organization criteria for MCL (Swerdlow *et al*, 2008), and were untreated at inclusion in the trial. All samples underwent central pathology review. The MCL2 protocol was approved by the national medicine agencies and science ethics committees in Denmark, Norway, Sweden and Finland. Informed consent was obtained from all patients. Patient characteristics are shown in Table I.

Treatment

The treatment regimen has been described previously (Geisler *et al*, 2008). The patients received alternating courses of maxi-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and high-dose Ara-C, 3 of each. Rituximab was co-administered on day 1 in cycles 4 and 5, and on days 1 and 9 in cycle 6. After an amendment in 2003, rituximab was administered also in cycles 2 and 3. A stem cell harvest was performed after cycle 6. Either BEAM (carmustine, etoposide, Ara-C, melphalan) or BEAC (carmustine, etoposide, Ara-C, cyclophosphamide) was used as a high-dose regimen before ASCT. During the first 5 years of follow-up, minimal residual disease (MRD) was assessed by polymerase chain reaction (PCR) for either the clonal *IGH* rearrangement or translocation t(11;14). Patients still in clinical complete remission (CR), who converted from

Table I. Characteristics of the 159 patients with mantle cell lymphoma.

| Patient-specific variables | n (%) |
|---|----------|
| Male gender | 113 (71) |
| Age (years): median | 56 |
| Range | 32–65 |
| Stage IV | 136 (85) |
| Splenomegaly | 72 (45) |
| Extranodal disease other than bone marrow | 50 (31) |
| MIPI risk groups (<i>n</i> = 157)* | |
| low | 79 (50) |
| intermediate | 41 (26) |
| high | 37 (24) |
| Disease-specific variables | |
| Cytological variant | |
| Blastoid/pleomorphic | 31 (20) |
| Common | 128 (81) |
| Growth pattern (<i>n</i> = 151) | |
| Nodular | 26 (16) |
| Mantle | 5 (3) |
| Mixed | 39 (25) |
| Diffuse | 81 (51) |
| Ki-67 expression (<i>n</i> = 120) | |
| 0–9% | 10 (8) |
| 10–29% | 60 (50) |
| >29% | 50 (42) |

*MIPI, Mantle Cell Lymphoma International Prognostic Index.

PCR-negative to PCR-positive bone marrow or blood, were offered pre-emptive therapy with rituximab 375 mg/m² weekly for 4 weeks, to prevent clinical relapse.

Statistics

The statistical assessments and endpoints were performed according to the National Cancer Institute guidelines (Cheson *et al*, 2007). Overall survival (OS), progression-free survival (PFS) and cumulative incidence of relapse (CIR) were based on an intent-to-treat principle and measured from the first day of induction therapy. Subanalyses were used to stratify patients based on response to induction regimen. As for OS, the endpoint was death from any cause, whereas for PFS it was lymphoma relapse/progression or death from any cause. The endpoint of CIR was MCL-progression or relapse. Survival curves were made according to the Kaplan–Meier method, and comparisons were made by log rank tests. Patients who were lost to follow-up were censored from the date and status when last known to be alive.

Mantle Cell Lymphoma International Prognostic Index and MIPI-B were assessed according to Hoster *et al* (2014), while the MIPI-B including miR-18b expression (MIPI-B-miR) was assessed according to Husby *et al* (2015).

A multivariate Cox regression analysis was performed to assess the effect on the outcome of pretreatment prognostic factors (age, sex, Ki-67 expression, cytological variant and

MIPI) as well as of the response to induction treatment, in terms of OS and PFS.

Moreover, we estimated expected survival in individuals comparable to the MCL patients (with respect to age, calendar year of follow-up, sex and country of origin) using data from the Human Mortality Database (<http://www.mortality.org>). The expected survival aims to mimic the survival of the MCL patients, had they not acquired MCL. An observed difference between the OS of the patients and the expected survival in the general population is indicative of excess mortality (directly or indirectly) attributable to MCL among the patients. To investigate long-term excess mortality we re-estimated the expected survival and OS of the patients in the subsets of patients who were alive and progression-free at 1, 5 and 10 years, respectively. Poisson regression was used to test if the observed excess mortality rate was significantly different from zero.

A *P*-value <0.05 was considered statistically significant.

Results

Characteristics of the 160 patients included in the study are presented in Table I. Since the last update (Geisler *et al*, 2012), one patient was excluded due to change of diagnosis. After adjusting for this, the overall response rate (ORR) after the induction treatment was 96% (54% in CR/unconfirmed CR [CRu]). One hundred and forty-five (91%) patients proceeded to ASCT and hereof, 130 (89.7%) achieved a CR or CRu post-ASCT.

Overall and progression-free survival

With a median follow-up time of 11.4 years (range 4.9–14.7), the median OS and PFS for all 159 patients were 12.7 and 8.5 years, respectively (Fig 1A, B, Table II). Of the 145 patients who proceeded to ASCT, the median OS was not reached and median PFS was 11.0 years (Table II). Stratified by pre-ASCT response, patients who had achieved a CR/CRu upon induction therapy demonstrated significantly better OS and PFS than patients in partial remission (*P* = 0.0038 for OS, *P* < 0.0001 for PFS) (Figure S1A, B). Five patients achieved CR after induction treatment, but did not proceed to ASCT (2 due to harvest failure, 1 due to heart failure, 2 for unknown reasons). Of these, all five relapsed quickly with a median PFS of 2.2 years (range 0.44–5.0 years).

Late relapses

All survival curves showed late events and convincing plateaus were not observed. Half of all patients had either progressed or relapsed at 12.0 years (Fig 1C), and we observed a continuous pattern of relapse throughout the follow-up, including relapses later than year 10 (Fig 1C). Of 93 patients still in first CR at 5 years, 18 relapsed later and, to date, 6 patients have relapsed beyond 10 years. Interestingly, of these

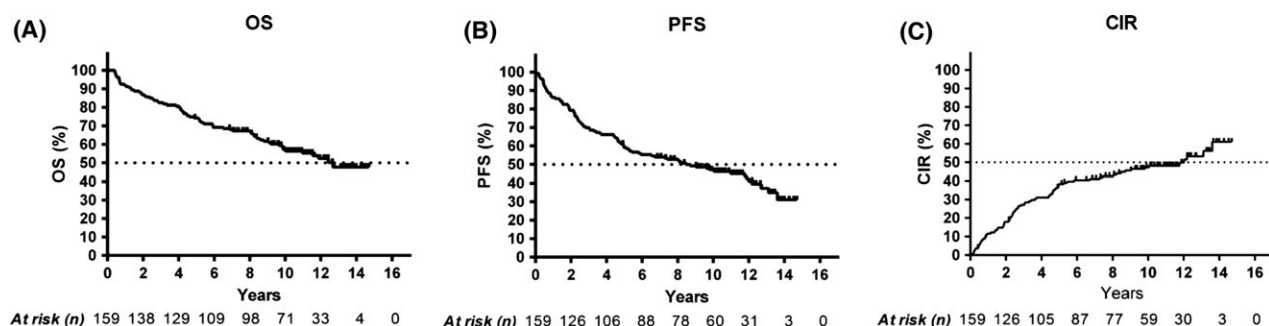


Fig 1. Updated follow-up for the Nordic MCL2 trial for (A) Overall survival (OS), (B) progression-free survival (PFS) and (C) cumulative incidence of relapse (CIR) after an intent-to-treat principle.

Table II. OS and PFS for patients enrolled in the Nordic MCL2 trial.

| | All intent-to-treat | | | All completed ASCT | | |
|--------------|---------------------|---------------|----------------|--------------------|---------------|----------------|
| | <i>n</i> (%) | OS (years) | PFS (years) | <i>n</i> (%) | OS (years) | PFS (years) |
| All | 159 | 12.7 | 8.5 | 145 | NR | 11.0 |
| MIPI | 157 | 12.7 | 8.5 | 143 | NR | 11.0 |
| <i>P</i> | | <0.0001 | <0.0001 | | <0.0001 | 0.0001 |
| low | 79 (50) | NR | 12.7 | 73 (51) | NR | 13.1 |
| intermediate | 41 (26) | 11.0 | 8.0 | 39 (27) | 11.0 | 8.2 |
| high | 37 (24) | 4.0 | 2.5 | 31 (22) | 5.3 | 2.7 |
| MIPI-B | 118 | 12.4 | 8.1 | 109 | 12.7 | 10.0 |
| <i>P</i> | | <0.0001 | 0.0009 | | 0.0008 | 0.0083 |
| low | 25 (21) | NR | 12.7 | 24 (22) | NR | 12.7 |
| intermediate | 38 (32) | NR | 11.8 | 36 (33) | NR | 11.9 |
| high | 55 (47) | 5.2 | 2.7 | 49 (45) | 8.3 | 4.6 |
| MIPI-B-miR | 61 | 12.4 | 6.5 | 55 | 12.4 | 8.5 |
| <i>P</i> | | <0.0001 | <0.0001 | | <0.0001 | <0.0001 |
| low | 30 (49) | NR | 13.1 | 29 (53) | NR | 13.1 |
| intermediate | 21 (34) | 8.3 | 4.6 | 19 (35) | 8.4 | 4.6 |
| high | 10 (16) | 1.6 | 1.0 | 7 (13) | 2.1 | 1.4 |

ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival. All presented as median values. MIPI, Mantle Cell Lymphoma International Prognostic Index; MIPI-B, biological MIPI including Ki-67 expression; MIPI-B-miR, MIPI algorithm including miR-18b expression.

17 late relapses, only 2 were MIPI high-risk patients, and no high-risk patients relapsed beyond 8 years (Fig 2B, Figure S2). Nine relapsing patients, of whom 5 patients are still alive, have undergone allogeneic stem cell transplantation during follow-up.

Prognostic factors

Both MIPI (available for 157 Patients) and MIPI-B (available for 119 patients) significantly separated patients into risk groups with regards to OS and PFS (Fig 2A–D, Table II). In general, we observed a continuous occurrence of relapses in all risk groups (Figure S2). From a recent publication on the same cohort we had available miR-18b expression on 62 patients (Husby *et al*, 2015) (Fig 2E, F and Figure S2). The MIPI-B-miR also separated the OS and PFS curves significantly ($P < 0.0001$ for all three endpoints), and furthermore

defined a high-risk group with inferior outcome as well as a low-risk group with superior outcome compared to the respective groups defined by MIPI and MIPI-B (Table II).

In univariate analyses, Blastoid/pleomorphic cytology showed a trend towards inferior OS ($P = 0.096$), but no influence on PFS ($P = 0.38$) (Figure S3A, B). In multivariate analyses ($n = 119$) MIPI showed significant prognostic impact on both OS and PFS ($P < 0.0001$ and $P = 0.0001$, respectively), whereas the cytological variant (blastoid or pleomorphic) had borderline negative influence on OS ($P = 0.0945$), but not PFS.

Excess mortality

The overall survival of the MCL patients was significantly lower ($P < 0.001$) when compared to the expected survival in the general population (Fig 3A). A similar pattern was

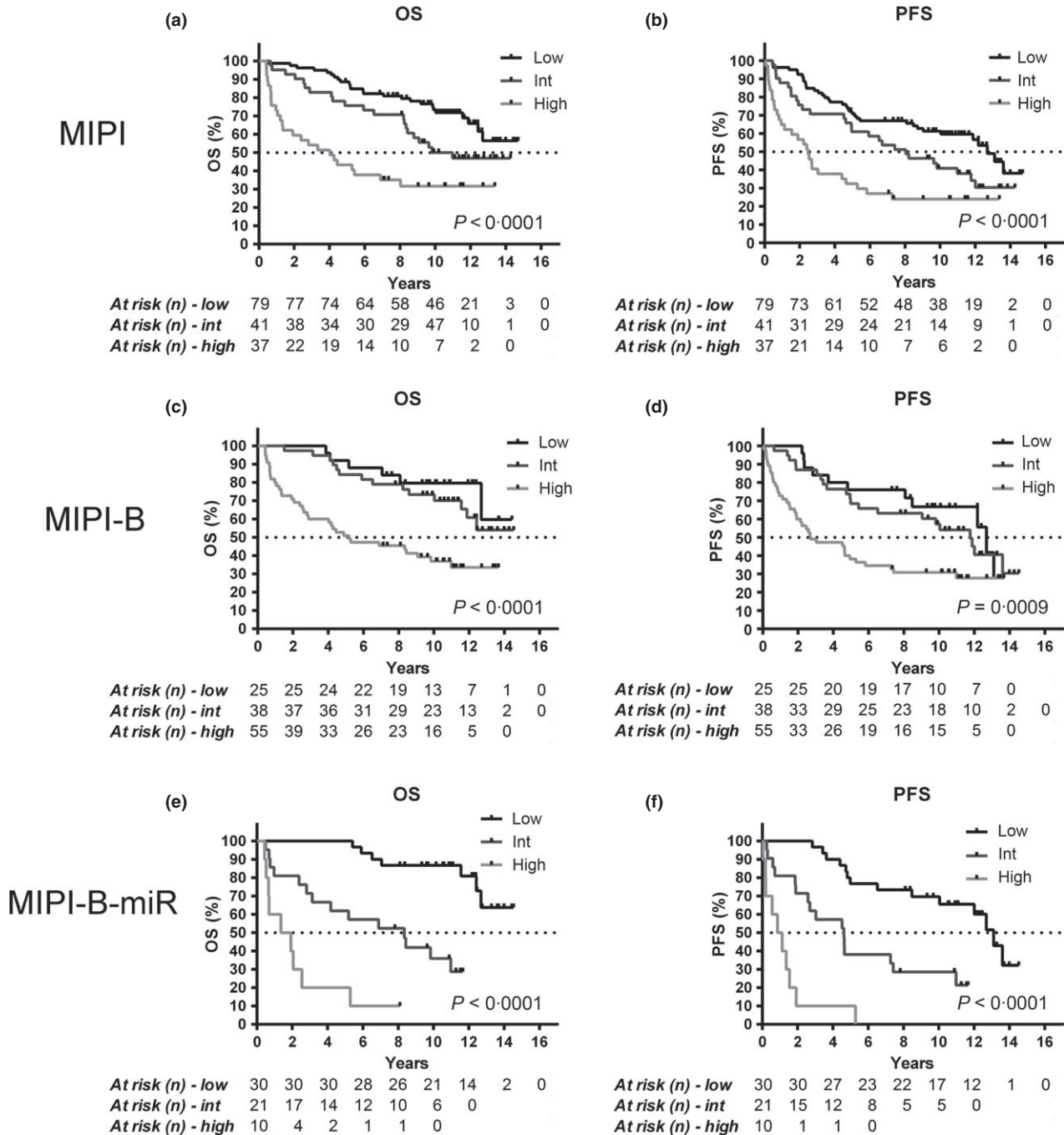


Fig 2. Stratification of overall and progression-free survival for MCL2 cohort according to the mantle cell lymphoma prognostic indexes. (A, B) Mantle Cell Lymphoma International Prognostic Index (MIPI), (C, D) biological MIPI including Ki-67 expression (MIPI-B) and (E, F) MIPI algorithm including miR-18b expression (MIPI-B-miR).

also observed when further stratifying the patients by MIPI, MIPI-B and MIPI-B-miR (data not shown). When comparing the survival of patients still in first CR after 1, 5 and 10 years to the expected survival in a comparable group from the general population there was still evidence of excess mortality, although a smaller difference was found with longer time in first CR (Fig 3B–D). In the 59 patients in remission

after 10 years, only 4 deaths were reported and no deaths were MCL related; however, 6 MCL relapses occurred.

Late toxicities

Since the last update in 2010 (Geisler *et al*, 2012), 11 new cases of other malignancies have been reported (excluding

non-melanoma skin cancers), thus reaching a total of 20, including 15 solid tumours (9.4%) (nasopharyngeal: 1, lung: 1, breast: 2, oesophagus: 1, stomach: 1, bile duct: 1, colon: 2, kidney: 1 prostate: 4, ovarian: 1). Five myeloid malignancies (3.1%) (3 myelodysplastic syndrome [MDS] and 2 acute myeloid leukaemia [AML]) have been reported and 4 of these had received additional chemotherapy for MCL relapse prior to diagnosis of MDS/AML.

Discussion

We present the updated results of the Nordic MCL2 trial after the longest follow-up to date of a state-of-the-art front-line treatment regimen of younger MCL patients including ASCT. Half of the patients are alive more than 12 years after the end of treatment and 40% are still in their first remission. However, there is continuous pattern of relapse, and an excess mortality persists even after long-term remission.

Our results are in agreement with two other multicentre studies with comparable regimens. Delarue *et al* (2013) used CHOP + rituximab (R-CHOP) and R-DHAP (rituximab, dexamethasone, high-dose Ara-C, cisplatin) followed by ASCT and produced similar response rates. After a median

follow-up of 5.6 years the median event-free survival was 6.9 years and the 5-year survival rate was 75% (comparably, the 5-year survival rate in our study was 74%). In the European MCL Network trial the median failure-free survival was 7.3 years for the superior regimen (R-CHOP/R-DHAP + ASCT) (Hermine *et al*, 2012), while the median OS had not been reached after a median follow-up of 4.3 years.

In 2015, the MD Anderson group (Chihara *et al*, 2015) presented updated results for the use of hyper-CVAD/Ara-C/Methotrexate (MTX) without ASCT; after a median follow-up of 13.4 years the median failure-free survival was 6.5 years and OS was 13.4 years. These data are thus comparable to ours and confirm the importance of intensive Ara-C-containing regimens. However, the high response rates have not been fully reproducible in multicentre studies (Merli *et al*, 2012; Bernstein *et al*, 2013), and compared to the European approaches, the hyper-CVAD/Ara-C/MTX approach seems to be a more toxic regimen (Romaguera, 2005; Geisler *et al*, 2008; Merli *et al*, 2012; Bernstein *et al*, 2013; Delarue *et al*, 2013).

Other induction regimens have been proposed. Both Visco *et al* (2013) and Armand *et al* (2016) presented very high response rates using a regimen consisting of rituximab,

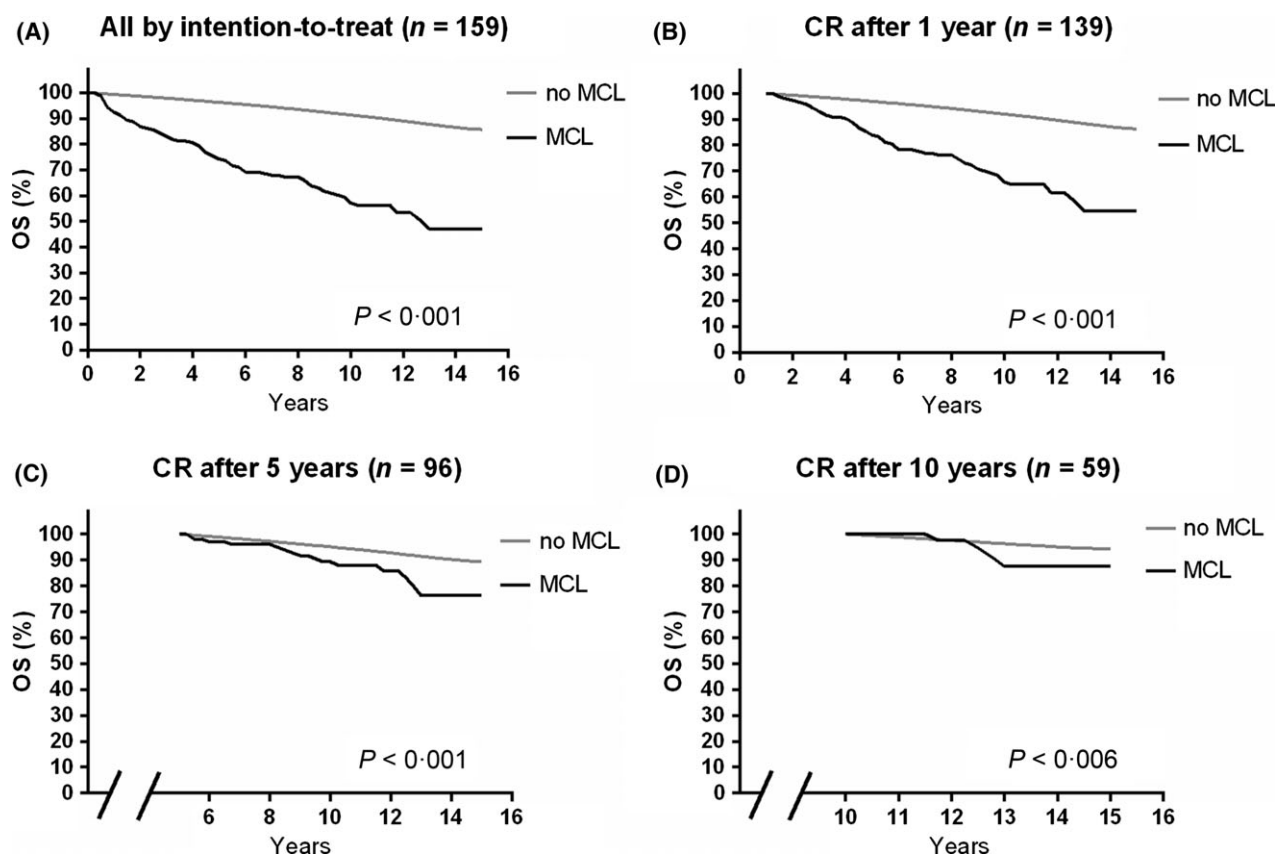


Fig 3. Conditional survival of the MCL2 patients compared to the estimated survival, had they not acquired MCL (based on data from the Human Mortality data base; <http://www.mortality.org>). (A) All patients. Patients in first complete remission after (B) 1 year, (C) 5 years and (D) 10 years, respectively. In (C) and (D) the x-axis has been adjusted to match the curves starting at 5 and 10 years, respectively. MCL, Mantle cell lymphoma; CR, complete remission; OS, overall survival.

bendamustine and Ara-C, although these studies only included a small number of patients.

The contribution of high-dose chemotherapy and ASCT to an optimal Ara-C containing induction regimen has not been addressed in controlled trials. The European MCL Network trial compared ASCT to interferon- α maintenance after CHOP-like induction and demonstrated a prolonged PFS, however with no significant improvement of the OS (Dreyling *et al*, 2005). The newly launched Triangle trial will investigate the benefit of ASCT after an optimal rituximab- and Ara-C-containing induction plus ibrutinib (Dreyling & Ferrero, 2016). Until then, ASCT-containing regimens are still considered standard-of-care for younger patients in Europe (Robinson *et al*, 2015).

To thoroughly address the MCL-related survival of the patients, we matched each patient with controls from the general population as described in the material and methods section (Fig 3). As expected, patients displayed an excess mortality in all prognostic subgroups; however, with apparent decreasing rates after longer time in remission.

The MIPI and MIPI-B still significantly divide patients into three distinct groups, of which the high-risk groups show a grave prognosis with refractory disease and early relapse. The low/intermediate-risk groups demonstrate impressive response durations, but unfortunately, as we show here, a continuous occurrence of relapses and, similarly, the survival curves never reach a plateau (Fig 2A–D and Figure S2).

This report updates our recent demonstration that miR-18b expression significantly improves the MIPI-B prognostication (MIPI-B-miR) (Husby *et al*, 2015). A highly significant separation of the curves remains, and the high-risk patients in particular have an exceedingly poor prognosis (Fig 2E, F). Ongoing studies in our group are seeking to unravel the function of miR-18b.

In a large observational study by the NLG including 1389 MCL patients from 2000 to 2011 (including the MCL2 patients) (Abrahamsson *et al*, 2014), gender was shown to be an individual prognostic factor in multivariate analyses, favouring women. This, however, was not the case in this isolated MCL2 cohort, and only MIPI showed independent significant impact.

Throughout the follow-up, 5 cases (3.1%) of secondary myeloid malignancies were reported. Of these 5 patients only 1 was still in first CR, while the remaining 4 had been exposed to relapse treatment and thus received a higher cumulative dose of chemotherapy. Comparably, in the hyperCVAD/Ara-C/MTX setting, 6.2% of patients in first CR experienced a myeloid malignancy after a median follow-up of 13.4 years (Chihara *et al*, 2015). Thus, consolidation with BEAM/BEAC plus ASCT (as in our trial) does not appear to increase the risk of secondary myeloid malignancies.

At present, the treatment of MCL is in transition with many novel targeted agents in development, and the challenge now seems to be *how* rather than *if* they should be incorporated in

the first-line treatment. One such agent is Ibrutinib, which has produced impressive response rates in the relapse setting (Wang *et al*, 2013), and thus has been included in the European MCL Network's "Triangle" trial of untreated MCL patients (EudraCT Number 2014-001363-12) (Dreyling & Ferrero, 2016). But until convincing data emerge, the standard-of-care remains an Ara-C containing induction plus rituximab, followed by high dose chemotherapy and ASCT (Robinson *et al*, 2015). More than half of the patients in the MCL2 trial are still alive after more than 12 years.

In conclusion, despite prolonged remissions, a continuous pattern of relapses has occurred throughout the follow-up, and there is an excess mortality among all MCL patients even after long-term remissions. This underlines the importance of participating in prospective trials to explore the possible benefits of novel agents in first line treatment of MCL.

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Author contributions

Creation and execution of the protocol: AK, MJ, RR, AL, LBP, NSA, ME, EK, HB, OK, GFL, HNE, ER, ME, CS, JD, MLKL, EE, PB, CHG via the Nordic Lymphoma Groups plenary meetings; Analysed the data: CWE, CHG, KG, PB, SE, KES, SH, CG and CTW. Drafting of the manuscript: CWE, CHG, KG. Critical review of manuscript: All authors.

Conflict of interest

The authors declare no competing financial interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Updated follow-up of the Nordic MCL2 trial for the 145 patients who proceeded to autologous stem cell transplantation (ASCT), stratified by response (CR/CRu or PR) pre-ASCT. (A) Overall survival (OS) and (B) progression-free survival (PFS).

Fig S2. Cumulated incidence of relapse (CIR) of patients from the Nordic MCL2 trial, stratified by the MCL prognostic indexes (A) MIPI, (B) MIPI-B (C) MIPI-B-miR.

Fig S3. (A) overall and (B) progression-free survival of patients from the Nordic MCL2 trial according to cytology in diagnostic samples (Blastoid/pleomorphic “Blastoid” or non-blastoid/pleomorphic “non-Blastoid”).

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