Safety, efficacy and tolerability of the NORDIC regimen in the front-line treatment of transplant-eligible patients with mantle cell lymphoma

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Background and study aims

- Mantle cell lymphoma is a mature B cell neoplasm comprising 3-10% of all Non-Hodgkin lymphomas.
- It is incurable with standard therapies, with an historic median survival of 4-5 years.
- The use of high-dose therapy and autologous stem cell transplantation (ASCT) has significantly improved outcomes in younger (<65), fitter and transplant-eligible patients.
- There is growing evidence that cytarabine-based induction regimens offer a survival advantage in this group of patients - however, there is no gold standard induction regimen for these patients, and centres vary in their choices depending on local experience.
- The NORDIC regimen involves administering rituximab and augmented CHOP (R-maxiCHOP) alternating with high dose cytarabine, followed by a BEAM autograft (Figure 1); 15-year follow up of this regimen has shown median survival of up to 12.6 years. However, this improvement in survival comes at a cost of increased toxicity, including early death and secondary malignancies.
- We aimed to evaluate the real-life safety, efficacy and tolerability of this regimen based on our patient cohort at a large District General Hospital (Royal Derby Hospital).

The NORDIC regimen

Cycle	Treatment
1	MaxiCHOP
2	Rituximab + high dose cytarabine
3	Rituximab + MaxiCHOP
4	Rituximab + high dose cytarabine
5	Rituximab + MaxiCHOP
6	Rituximab + high dose cytarabine + additional rituximab
→	Proceed to BEAM-conditioned autograft according to response

Figure 1: Example sequence of chemotherapeutic treatments under the NORDIC regimen.

Patient characteristics

Total number	Male: Female	Age at diagnosis (years)	Stage at presentation	MIPI Score	Median follow-up period post-treatment
N = 22	13:9	Mean = 59.3 Range = 50.0 - 70.7	Stage 3 (n = 3) Stage 4 (n = 18) Not documented (n = 1)	Mean = 5.6 Range = 2.0 - 8.5	3.4 years

Figure 2: Patient characteristics:
In total, 22 patients (13 male, 9 female) were treated with the NORDIC regimen between 2012 - 2018. All of those for whom case notes were available had stage 3 or stage 4 disease at diagnosis. A Mantle Cell Lymphoma International Prognostic Index (MIPI) score was documented for 16 patients. Data regarding patient outcomes was collected in 2019 - the median amount of time for which patients were followed up post-completion of NORDIC treatment was 3.4 years.

Results: outcomes

Total number of patients	n = 22
Deaths during treatment on NORDIC	n = 2
Deaths (total)	n = 3
Mean MIPI of decedents	7.5
Mean age of decedents	64.6
Relapsed post-NORDIC	n = 16
Patients completing NORDIC	n = 18
Proceeded to autograft	n = 16
Remission status - complete remission	n = 17
Remission status - lost to follow up	n = 2

Figure 3: Patient outcomes:
Of the 22 patients followed up, three patients died (14%). Two deaths occurred during treatment with the NORDIC regimen, with one further occurring after treatment escalation. Decedents tended to be older, with a higher MIPI score at diagnosis than average, though the analysis was not sufficiently powered to comment on the significance of these observations. Eighteen patients (82%) completed the NORDIC regimen, as one patient's treatment was stepped down due to recurrent sepsis. Of these, all patients for whom records were available were in complete remission at the time of analysis.

Results: tolerability

Total number of patients	n = 22
Number of chemotherapy cycles delayed	Mean = 0.7, SD = 0.8
Inpatient admissions	Mean = 3.0, SD = 3.0
Admissions with neutropaenic sepsis	Mean = 1.8, SD = 2.5
Intensive care unit admissions	Mean = 0.0, SD = 0.0
Units of packed red cells transfused	Mean = 7.3, SD = 9.0
Pools of platelets transfused	Mean = 1.9, SD = 3.7
Dose alterations or reductions	n = 4
Received maintenance rituximab	n = 14
Maintenance rituximab discontinued	n = 4

Figure 4: Tolerability of the NORDIC regimen:
Eighteen patients (82%) experienced at least one unscheduled inpatient admission during treatment with the NORDIC protocol, of which 14 patients (64%) were admitted for neutropaenic sepsis at least once. Nineteen patients (86%) required at least one type of transfusional support during treatment. Only three patients (14%) completed the NORDIC protocol without any delays or alterations to chemotherapy cycles. Dose modifications were authorised in four patients (18%) due to toxicity and medical comorbidities. These included a dose reduction in high dose cytarabine, and an anthracycline dose reduction due to poor cardiac function.

Interpretation and conclusions

- Overall, these data suggest that although the NORDIC regimen is reasonably well-tolerated and efficacious in the majority of patients, there is considerable associated morbidity and toxicity.
- More long-term follow-up of a larger patient cohort is required to look at overall survival and late toxicity.
- Furthermore, similar data from comparable regimens such as RDHAP (rituximab, dexamethasone, cytarabine and cisplatin) would enable clinicians to make a more informed choice of front-line therapy in these younger patients.
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