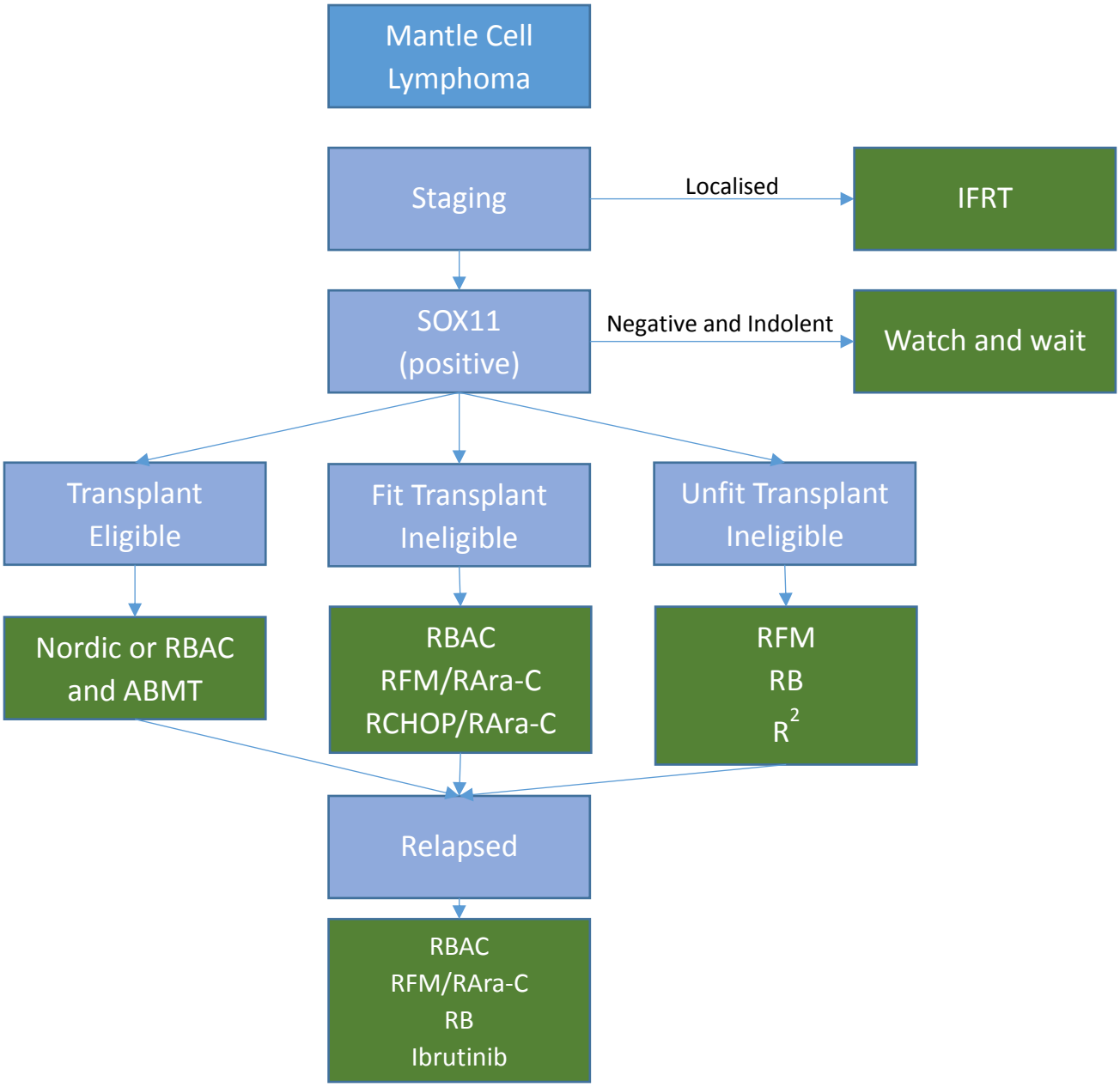
Lymphoma Network of New Zealand

Mantle Cell Lymphoma (MCL) Protocol



1. Introduction

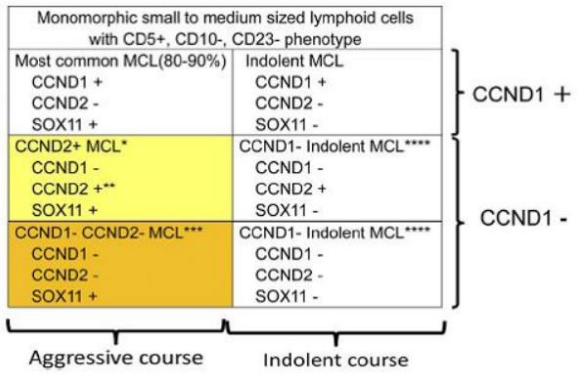
MCL accounts for approximately 6% of all cases of NHL. The median age of patients in New Zealand is 69, with approximately 2:1 male to female ratio. . There are about 40 new cases/year diagnosed in New Zealand, with an icidence of about 1/100 000/year, which is similar to Nordic data. Most patients present with advanced stage disease at diagnosis

MCL has a variable course. A small number of patients can have an indolent disease course. However, the majority of MCL present with advanced stage and have an aggressive disease course. There has been an improvement in outcomes with more intensive therapy and the median survival is now more than 10 years in those under 65 and 60% at 4 years in the 65-75 yr olds.

More aggressive treatment strategies including consolidation with autologous transplants are aimed at improving outcome in this disease. Despite the long progression free survivals now seen, late relapses may occur, although there are now a reasonable number of patients who achieve a functional cure.

2. Pathology and Cytogenetics

MCL is thought to originate from the marginal zone or from a peripheral blood memory B-cell. The immunophenotype of the malignant cells in MCL is typically CD20+, CD5+, CD10-, CD23-, with either kappa or lambda light chain cell surface expression. CD200 is absent or dim which can be helpful in distinguishing Mantle Cell Lymphoma from CLL (which is CD200+) The majority of MCL express cyclin-D1 protein in the tumor cells as a result of a translocation of the cyclin-D1 gene (CCND1) on 11q13 to the promoter of the heavy chain locus on 14q32. But there are 6 subtypes which express Cyclin D1, D2 or neither (mostly expressing cyclin D3) and that either express SOX11 or do not. SOX11 expression is usually positive and associated with an aggressive clinical course and these mantle cells have an unmutated IgH. About 10% of MCL have an indolent course, do not express SOX11 and have a mutated IgH. Cyclin D1 negative MCL can also be SOX11 positive or negative and appears to have a similar prognosis and response to treatment as Cyclin D1 positive cases. (Itziar Salaverria, 2013) (Seto, 2013) A subgroup of MCL have immature morphology – so called Blastoid variant.



3. Staging Investigations

Staging investigations include routine CT scanning of chest, abdomen, pelvis, +/- neck and bone marrow biopsy. Asymptomatic GI involvement is common, consideration should be given to upper and lower GI endoscopy if clinically appropriate, although this is not necessary in most cases. The Ann Arbor staging system is used.

4. Prognosis

4.1 IPI/MIPI score

The IPI can be used for mantle cell lymphoma butthe MIPI is designed specifically for advanced stage mantle cell lymphoma, it was then modified to include the Ki67 and MIPIb (Mantle cell lymphomainterational prognostic index combined biologic incidence. (Hoster E, 2008)

MIPI

Points	Age (Years)	ECOG	LDH ratio to ULN	WBC
0	<50	0-1	<0.67	<6.7
1	50-59		0.67-0.99	6.7-9.99
2	60-69	2-4	1-1.49	10-14.99
3	>70		>1.49	>14.99

- Low risk 0-3
- Intermediate 4-5
- High 6-11

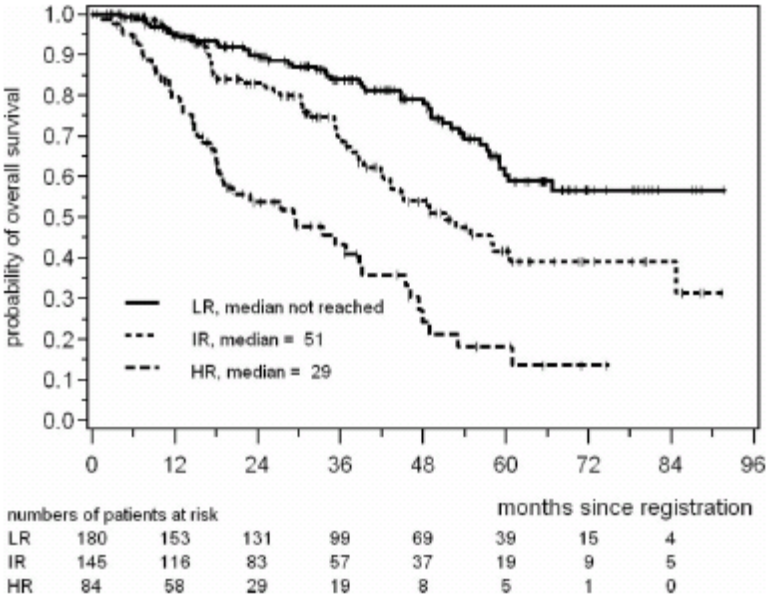


Figure 3. Overall survival according to the new prognostic index (MIPI). LR indicates low risk, prognostic score less than 5.7; IR, intermediate risk, score 5.7 or more but less than 6.2; and HR, high risk, score 6.2 or more. The prognostic score is calculated as [0.03535 × age (years)] + 0.6978 (if ECOG > 1) + [1.367 × $\log_{10}$(LDH/ULN)] + [0.9393 × $\log_{10}$(WBC count].

4.2 Ki67

Ki67 has independent strong prognostic relevance (Determann O, 2008)

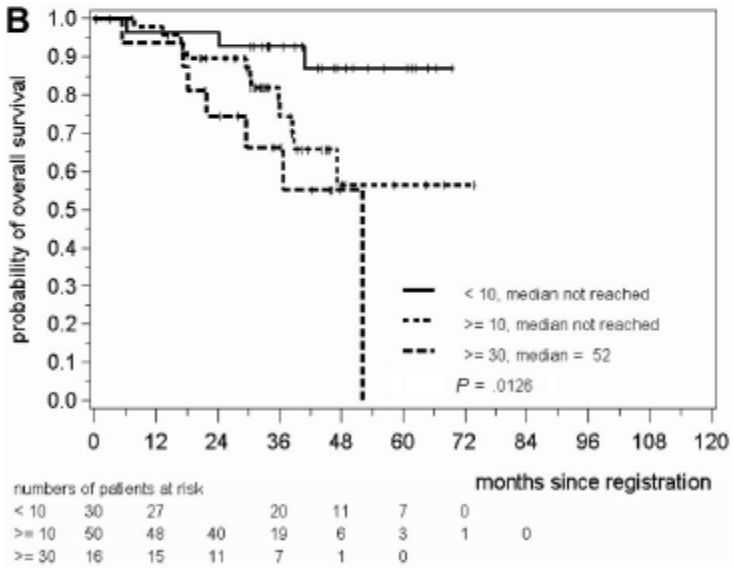


Figure 1. Kaplan-Meier plot for overall survival of patients treated with CHOP (A) and R-CHOP (B) stratified in 3 groups according to the Ki-67 index of less than 10% (< 10), 10% to less than 30% (≥10), and 30% or more (≥30) Ki-67 positive cells.

4.3 Blastoid Variant

This also predicts for poorer survival.

5. Rationale for Therapy

Where possible, cases should be enrolled in clinical trials**.**

5.1 Localised Disease

Diagnosis of localized disease requires full staging investigations including consideration of UGI and lower GI endoscopy. Only a minority of patients present with localized disease and have better OS than for advanced stage disease. Patients with stage IA or IIA (non bulk < 10 cm) have an OS of 6.8 years. Radiotherapy has been shown to provide effective disease control in this group with superior outcomes to chemotherapy, and is the treatment of choice in this setting. Chemotherapy in addition to radiotherapy may provide additional benefit but numbers from studies are too small to draw firm conclusions. Cases should be considered on a case by case basis taking into account of potential treatment toxicities. (Leitch HA, 2003)

5.2 Role for Watch and Wait Strategy

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Patients who are negative for SOX11 usually have a lowKi67 of <10% and an indolent disease. A watch a wait approach is appropriate.

5.3 Management of Transplant Eligible patient

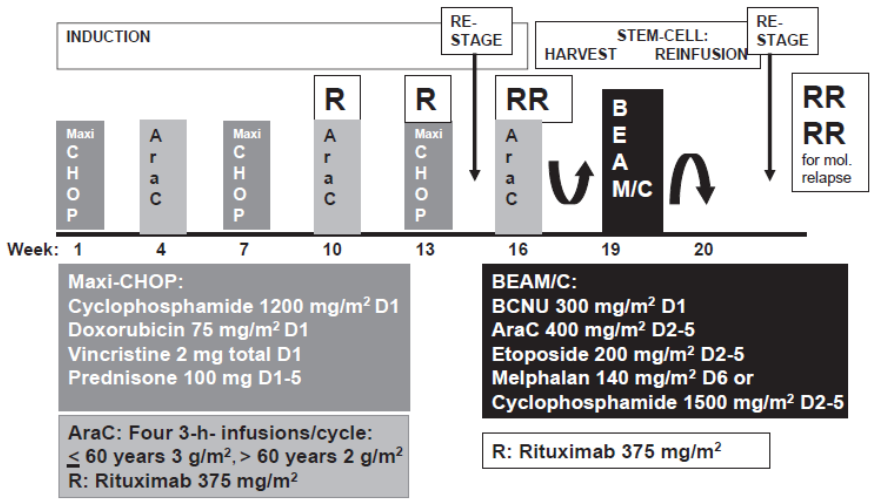
Intensifying treatment has improved outcomes in mantle cell lymphoma. An early approach was to use HyperCVAD MA, and the 16 year follow up data reported by the MD Anderson Cancer Center shows good long term outcomes. This regimen can be quite toxic and there is a cumulative incidence of MDS/AML of 5-10% with the long term follow-up. This regimen affects the ability to mobilise stem cells and autologous transplant consolidation is not a feasible strategy. Other groups have used alternative approaches and a common theme is that high dose Ara-C containing regimens seem to show the best and most durable response rates.

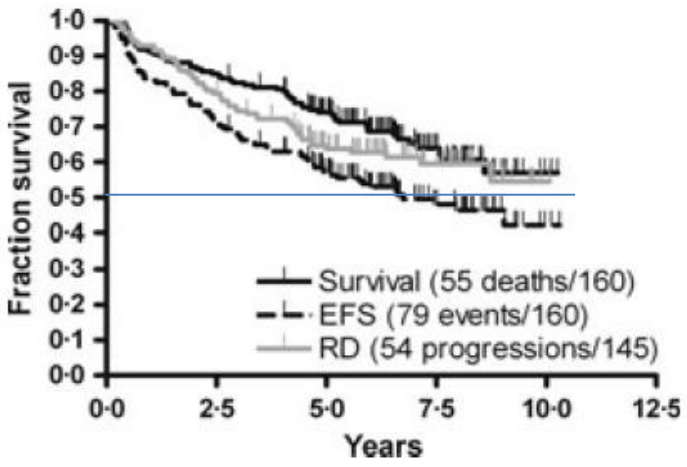
Large prospective studies of cytarabine intensification for first-line MCL

Regimen	Reference (year)	N	ORR, %	CRR, %	Toxicity grade III-IV
Hyper-CVAD/MTX-Ara-C	Khouri et al[50] (1998)	45 (20 untreated)	93	38	Thrombocytopenia 85%, infections 10%
Hyper-CVAD/MTX-Ara-C	Romaguera et al[58] (2000)	25 (age > 65 y)	92	68	Toxic death 8%, infections 5%
R-Hyper-CVAD/R-MTX-Ara-C	Romaguera et al[52] (2005)	97	97	87	Toxic death 5%, MDS 3%
R-Hyper-CVAD/R-MTX-Ara-C	Epner et al[53] (2007)	49	88	58	Toxic death 2%, hematotoxicity 87%
R-Hyper-CVAD/R-MTX-Ara-C	Merli et al[54] (2008)	32	53	50	Toxic death 6%, severe infections 15%
R-DHAP	de Guibert et al[57] (2006)	25	96	92	Thrombocytopenia 33%
CHOP × 3 + DHAP × 3	Lefrère et al[51] (2004)	28	92	84	—
R-CHOP × 3 + R-DHAP × 3	Delarue et al[55] (2008)	60	95	61	—
R-CHOP × 3 + HD-Ara-C × 1	van't Veer et al[56] (2008)	87	72	29	Infections 30%

The Nordic study protocol MCL-2 was reported on 159 newly diagnosed MCL patients stages II-IV age <66 years and shows five year EFS and OS of 63% and 74% respectively. Late relapses can occur and the 10 year PFS is about 40% and OS 55-60% . Treatment-related mortality is 3.8%. (Christian H. Geisler, 2012) (Geisler C)

Given significant toxicities associated with R-hyperCVAD the Nordic protocol is the locally preferred treatment option. Although with data showing R-CHOP is inferior to R-Bendamustine this regimen is unlikely to be optimal. (Mathias J Rummel, 2013) (Ian W. Flinn, 2014)





5.4 Management for Patients >65 years or PS ≥2

- The median age at diagnosis in New Zealand is 69 years so most patients are too old for stem cell transplant or high dose Ara-C as in the Nordic Protocol
- Frequently used conventional chemotherapy regimens have been R-CHOP, R-CVP, or R-FM. There have been two randomised studies comparing R-Bendamustine with R-CHOP (STiL study) and R-CHOP/R-CVP (Bright study). Both studies were in low grade lymphoma including Mantle cell lymphoma. Both showed superior response rates and PFS with R-Bendamustine in the mantle cell lymphoma subset.
- Given Ara-C is an effective agent in younger patients. Adding Ara-C to RCHOP (population based data from Nordic group) or to R-Bendamustine (R-BAC) seems to improve responses.
- The addition of rituximab appears to lead to higher response rates and progression free survival although the effect on OS is uncertain.
- Maintenance Rituximab has been shown to improve survival following R-CHOP but does not improve survival after R-Bendamustine (ASCO 2016)
- Response rates with R^2 Regimen (Rituximab and Lenalidomide) are high and this regimen is well tolerated in older patients.

The preferred treatment option based on published data is R-BAC in those patients able to tolerate Ara-C and R-Bendamustine in older patients or those with renal impairment. Bendamustine is not currently funded. R-CHOP/R-CVP are less effective. There is anecdotal experience with R-FM, which may be similar to R-Bendamustine, this can be given in alternating cycles with outpatient R-Ara-C (1g/m^2 D1 and 2).

- Treatment options include rituximab containing combination chemotherapy regimens including:
  - R-BAC

    R-Bendamustine

    R-FM/R-Ara-C
  - RFM

    R-Lenalidomide
  - RCVP
  - RCHOP

Most chemotherapy regimens have not been compared directly and it is not possible to provide strong recommendations as to which is best nor to provide the optimal sequence of use of these regimens as initial therapy and at disease progression. Cases should be reviewed on a case by case basis.

5.5 Role of Radiotherapy in Advanced Disease

The benefit of RT in addition to chemotherapy in advanced disease in patients obtaining a CR is not proven.

5.6 Role of Allogeneic Transplant

Reduced intensity allogeneic transplantation has been reported with failure free survival and OS of 55% at 3 years. Complete remissions have been achieved in patients with relapsed disease. The activity of new agents means this approach is less appealing but it could be considered in younger patients with a suitable donor in first or second response and in those who have relapsed post autologous transplant.

5.7 Novel Agents for MCL

There are a number of new treatments that are showing activity in mantle cell lymphoma and are likely to change treatment approaches for this disease.

BTK Inhibitors

Ibrutinib (560mg daily), Acalbrutinib and BGB311 have all shown activity in heavily treated mantle cell lymphoma. Responses are likely to be higher and of longer duration when used earlier in the disease course

BH3 Mimetics/BCL2 inhibitors.

Venetoclax a BCL-2 inhibitor has shown significant activity in small numbers of patients.

PI3K inhibitors

PI3K inhibitors such as Idelalisib has also shown activity.

Bortezomib has also shown activity but less than other new agents, however, it is less costly coming off patent and more readily available.

6. Chemotherapy Regimes

6.1 Nordic Protocol

a. 3 cycles of maxi-R-CHOP alternating with 3 cycles of R-cytarabine
b. Interval between cycles 21 days
c. Followed by autologous stem cell transplant with BEAM conditioning (Geisler C) (Christian H. Geisler, 2012)

Maxi-CHOP

Cyclophosphamide	1200 mg/m^2 IV in 500 ml 0.9% NaCl over 60 minutes Day 1
Doxorubicin	75 mg/m^2 IV over 15-20 minutes Day 1
Vincristine	2 mg IV in 50 ml 0.9% NaCl over 5-10 minute infusion Day 1
Prednisone	100 mg PO Day 1-5
Rituximab	375 mg/m^2 IV infuse as per protocol Day 1 **(omitted in first cycle of Maxi-CHOP)**
G-CSF	Pegfilgrastim 6 mg SC on Day 4

- Neutrophils of >1x10^9/l and/or platelets of >75x10^9/l are required prior to starting subsequent maxi-CHOP. If cell numbers are too low, the chemo should be postponed and FBC monitored every 3/7. If acceptable levels are obtained within one week, the subsequent course of maxi-CHOP can be given with full dose. If platelets and neutrophils are still low, see dose modifications below.

Cytarabine Cycles 1 and 2	
Cytarabine	3 g/m^2 (2 g/m^2 for pts >60 years) IV every 12 hours for 2 days in 500 ml 0.9% NaCl given over 1 hour infusion
predsol eye drops	Starting 48 hours after first dose of cytarabine and continued until Day 4
Rituximab	375 mg/m^2 IV infuse as per protocol Day 1
G-CSF	Pegfilgrastim 6 mg SC on Day 4

- Neutrophils should be >0.5x10^9/l and or platelets >50x10^9/l prior to ara-c. When these values are not reached, the ara-c should be postponed until they are reached and then given at full dose.

Cytarabine for Cycle 3 – used for stem cell mobilisation	
Cytarabine	3 g/m^2 (2 g/m^2 for patients >60 years) IV every 12 hours for 2 days in 500ml 0.9% NaCl given as 1 hour infusion
predsol eye drops	Starting 48hrs after first dose of cytarabine and continued until Day 4
Rituximab	375 mg/m^2 IV infuse as per protocol Days 1 and 9

G-CSF	10 ug/kg/day SC from Day 4 until harvest complete

- A minimum of 2 x 10^6 CD34 cells/kg required.
- Those who do not mobilise an adequate number of stem cells from blood, a regular bone marrow harvest can be performed.
- When necessary for logistical reasons, patients can receive one additional course of maxi-CHOP with rituximab before start of high dose therapy.
- Those achieving an adequate harvest can then proceed to an autologous transplant with BEAM preparative regimen.

6.1.1 Dose Modifications

1. For myelosuppresion
    - Dose modifications of maxi-CHOP can be made when acceptable neutrophil and platelet limits are not reached after a one week delay.

neuts10^9/l	plts x0^9/l	cyclophos %	doxorubicin %	vincristine %	prednisone
>1 and	>75	100	100	100	100
0.5-1or	50-75	50	50	100	100
<0.5 or	<50	0	0	100	100

2. For renal impairment
    - In renal impairment, cytarabine dose requires reduction.

Creatinine Clearance	**Cytarabine Dose**
45-60ml/min	60%
31-45 ml/min	50%
<30ml/min	Discontinue consider alternative therapy

3. For liver impairment
    - If bilirubin >34, then reduce cytarabine dose by 50%.

4. For neuropathy
    - Grade 2 neuropathy – 50% dose reduction of vincristine
    - Grade 4 neuropathy – stop vincrisine in all further cycles

6.2 Rituximab Fludarabine Mitoxantrone (RFM)

RFM	
Rituximab	375mg/m^2 as per protocol Day 1
Mitoxantrone	10 mg/m^2 Day 1
Fludarabine	25mg/m^2 po Days 1-5 (round to nearest 10 mg, cytotoxic prescription) adjusted for creatinine clearance (**Calc Creat clearance/90 x dose)**
Cycles every four weeks	

6.2.1 Supportive cares

- Allopurinol
- Antiemetics consistent with a moderately emetogenic chemotherapy regimen (ondansetron + maxalon +/- ativan 1 mg)
- Cotrimoxazole 960 mg OD 3 x week for duration of therapy and 6 months after
- **IRRADIATION** of all cellular blood products lifelong for those receiving fludarabine
- No hydration required

6.2.2. Dose Adjustments

1. Myelosuppression
    - For patients commencing therapy with cytopenias, consideration to pegfilgrastim support and if severe initial dose reductions may be required on a case by case basis
    - For treatment related cytopenias, the following guideline can be used:
        - Neutrophils <1, platelets <57 delay 1-2 weeks
        - If after two week delay, values are unchanged, proceed at 50% of the dose
        - Consider G-CSF to maintain schedule

2. Dose adjustment for Fludarabine in patients with renal impairment.

    Fludarabine is metabolised to F-ara-A, which is 60% renally cleared. There is a linear relationship between F-ara-A clearance and creatinine clearance. (ref)

    Calc Creat clearance/90 x dose

3. **Hepatic Impairment**

- No dose reductions required.

6.3 Rituximab Fludarabine Mitoxantrone (RFM)/Rituximab Ara-C (RAra-C)

Alternate RFM and RAra-C for a total of 6 cycles (3 cycles of each)

RFM	
Rituximab	375mg/m^2 Day 1
Mitoxantrone	10 mg/m^2 Day 1
Fludarabine	25mg/m^2 po Days 1-5 (round to nearest 10 mg, cytotoxic prescription) adjusted for creatinine clearance (**Calc Creat clearance/90 x dose)**
Start R-Ara-C after four weeks	

RAra-C	
Rituximab	375mg/m^2 as per protocol Day 1
Ara-C	1000 mg/m^2 Day 1 and 2
Start R-FM after three weeks	

6.4 Rituximab Bendamustine Ara-C (RBAC)

For a total of 6 cycles (Carlo Visco, 2013)

Orally	
Rituximab	375mg/m^2 as per protocol Day 1
Bendamustine	70mg/m^2 Days 1 and 2
Ara-C	800 mg/m^2 Day 1,2 and 3
Cycles every four weeks	

6.5 Rituximab Bendamustine (RB)

For a total of 6 cycles (Ian W. Flinn, 2014) (Mathias J Rummel, 2013) (Mathias Rummel, 2016)

RB	
Rituximab	375mg/m^2 IV Day 1
Bendamustine	90mg/m^2 IV Days 1 and 2

Cycles every four weeks

6.6 Rituximab Lenalidomide (R^2)

For a total of 6 cycles (Jia Ruan, 2015)

R^2	
Rituximab	375mg/m^2 IV Weekly x 4 then 8 weekly x 5
Lenalidomide	25mg PO Days 1 to 21, reduce to 15mg D1-21 after rituximab stops
Cycles every four weeks	

6.7 Ibrutinib

Continue until disease progression

Ibrutinib	
Ibrutinib	560mg daily

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