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15

Mantle Cell Lymphoma: Decision Making for Transplant

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1. Introduction

1.1 Definition and clinical characteristics

Mantle Cell Lymphoma (MCL) is a relatively rare type of mature B-cell lymphoma that comprises 5% of Non-Hodgkin's Lymphomas(NHL)[1-3]. MCL was added to the Revised European–American Lymphoma classification in 1994. Having both indolent and incurable features associated with aggressive clinical course, MCL is most frequently seen in 6th decade of life, with male dominance 3 to 4:1[2]. Malignant origin of MCL cells appear to derive from an antigen-naive pregerminal center cell[4, 5].

1.	**B-cell neoplasms**
1.	Precursor B-cell
2.	Mature B-cell
	Chronic lymphocytic leukemia/small lymphocytic lymphoma
	Lymphoplasmacytic lymphoma
	Splenic marginal zone lymphoma
	Extranodal marginal zone B-cell lymphoma of MALT
	Nodal marginal zone B-cell lymphoma
	Follicular lymphoma
	Mantle cell lymphoma
	Diffuse large B-cell lymphoma
	Mediastinal (thymic) large B-cell lymphoma
	Intravascular large B-cell lymphoma
	Primary effusion lymphoma
	Burkitt's lymphoma/leukemia
3.	B-cell proliferations of uncertain malignant potential
2.	**T-Cell and NK-Cell neoplasms**

Table 1. World Health Organization Classification of Lymphomas[1].

At the time of diagnosis, patients tend to have more extranodal disease and low serum albumin[6]. Although MCL has differential diagnosis with Chronic Lymphocytic Leukemia (CLL) and low-grade NHL, mimicking malignancies with indolent behavior, it follows an aggressive course with 10% to 15% long-term survivors[7] despite administration of standard chemotherapy courses commonly used in NHLs[8], corresponding to a median survival of 3 to 5 years.

2. Diagnosis

Diagnosis of MCL can be made by lymph node or bone marrow biopsy, or analysis of malignant cells obtained from peripheral blood, if the disease is in the leukemic phase[9, 10]. Differential diagnosis with CLL is important since both MCL and CLL cell have co-expression of CD5 and CD19/20[11]. Malignant cells are negative for CD10, CD23 and BCL6. Although absence of CD23 antigen expression on malignant cell population strongly favor a diagnosis of MCL[12, 13], presence of cyclinD1 expression by immunohistochemical staining[14] or determination of t(11;14) translocation by molecular analysis[15-18] is required to confirm the diagnosis[19]. Cyclin D1 is overexpressed in MCL as a result of the landmark t(11;14)(q13;q32) translocation[20]. Cyclin D1 complex with cyclin dependent kinases 4 and 6 (Cdk4 and Cdk6) and cyclin E-Cdk2, leading to phosphorylation of retinoblastoma protein (Rb), irreversibly inducing progression of the cell from G1 to S phase, which is not the only biologic dysregulation on the way to malignant transformation[21-24].

Disease	**CD5**	**CD10**	**CD23**	**CD43**	**Cyclin D1**	**Ig class**
FL	-	+	+/-	-	-	IgM, IgG
MCL	+	-	-	+	+	IgM/IgD
CLL/SLL	+	-	+	+	-	IgM/IgD
LPL	-	-	-	+/-	-	IgM (c)
MALT	-	-	-	+/-	-	IgM (c, s)
SMZL	-	-	-	-	-	IgM/IgD
HCL	-	-	-	-	-/+	IgG

FL, follicular lymphoma; MCL, mantle cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; LPL, Lymphoplasmacytic lymphoma; MALT, marginal zone lymphoma of MALT type; SMZL, splenic marginal zone lymphoma; HCL, hairy cell leukemia; Ig class, most commonly expressed heavy chain classes; c, cytoplasmic Ig; s, surface Ig.

Table 2. Differential Diagnosis of "Small" B-Cell Lymphomas[25].

3. Prognostic parameters

Prognosis can be estimated by using MIPI (mantle cell lymphoma international prognostic index, Figure 1)[26] which seems to be more efficient than international prognostic index (IPI)[27] or follicular lymphoma international prognostic index (FLIPI)[28, 29], which includes leukemic phase[10, 30, 31], besides other clinical parameters used in the IPI.

Points	Age, y	ECOG	LDHULN	WBC, 10^9/L
0	<50	0-1	<0.67	< 6.700
1	50-59	—	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000 -1.49	1.000-14.999
3	≥70	—	≥1.5000	≥15000

Table 3. Simplified MIPI[26].

For each prognostic factor, 0 to 3 points were given to each patient and points were summed up to a maximum of 11. Patients with 0 to 3 points in summary were classified as low risk, patients with 4 to 5 points as intermediate risk, and patients with 6 to 11 points as high risk.

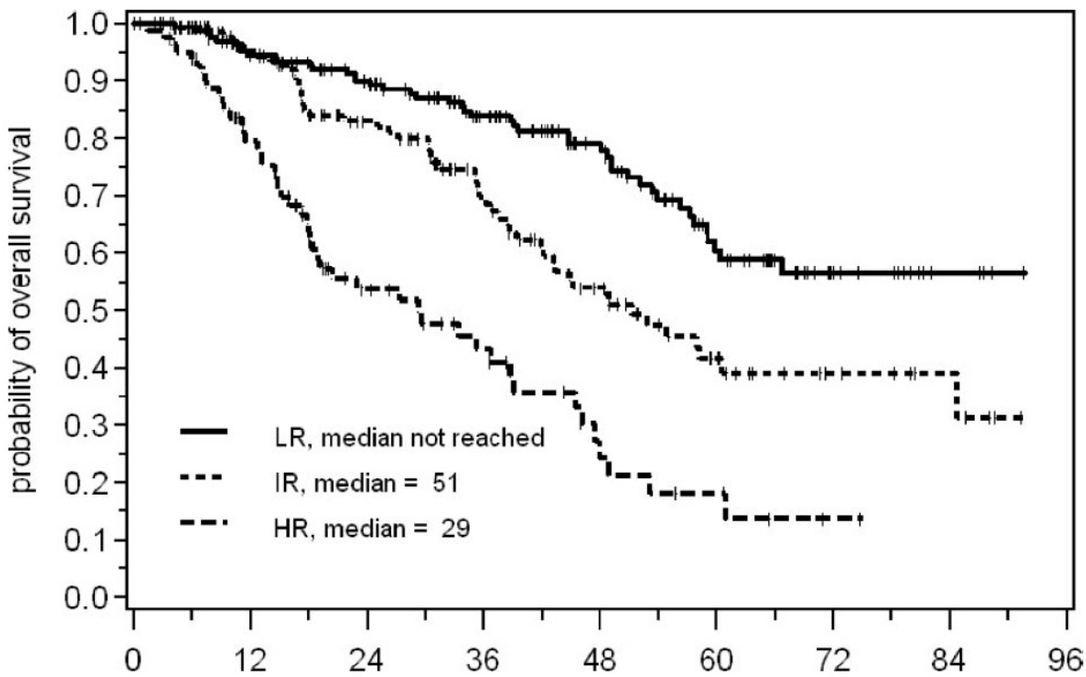

Fig. 1. Overall survival according to the mantle cell lymphoma international prognostic index (MIPI).

Although Ki-67 has previously been shown to predict prognosis (Figure 2)[32-34], analysis of Ki-67 did not substantially change the regression coefficient of the MIPI score and served as an important biologic marker with strong additional prognostic relevance[26].

Recently, proliferation gene expression signature has been reported to be the best molecular predictor of survival in patients with MCL[21], leading to a prognostic model defined as an optimized survival predictor composed of five genes: RAN, MYC, TNFRSF10B, POLE2, and SLC29A2[35]. Furthermore, this model was validated for application in formalin-fixed paraffin-embedded tissue samples and appeared superior to the immunohistochemical marker Ki-67[35].

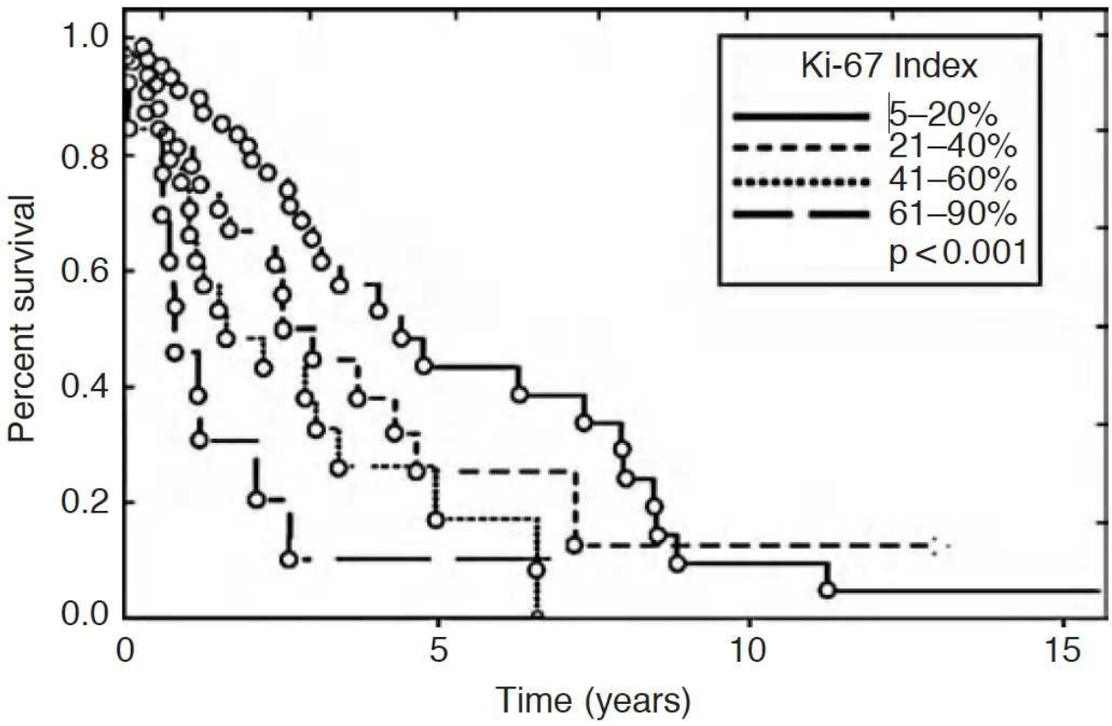

Fig. 2. Overall survival of patients with MCL according to Ki-67 proliferation index[33].

4. Role of chemotherapy

When it comes to assessment of long term overall survival, MCL has the worst prognosis among all lymphoma types[36], a watch-and-wait strategy should be avoided. Retrospective analyses of administration of standard chemotherapy have not shown any improvement in overall survival in patients with MCL[6, 37]. Most regiments induce around 80% response rates with complete remissions up to 30% of cases[6, 8]. While more aggressive regimens were used[38], reliable cure rates with conventional treatment has not been reported until now[36]. Compared to historical controls, median survival with conventional chemotherapy CVP and CHOP have not been improved[37]. In a randomized trial, these two regimens were associated with similar response rates (84% and 89%) and median overall survivals (32 and 37 months)[39]. Only one third of patients with untreated[40] or relapsed[41] MCL will respond to rituximab as single agent. Rituximab may also be used for purging tumor cells either with standard chemotherapy[42] or prior to high dose therapy regimens with stem cell support[43]. But in a randomized trial, addition of rituximab to CHOP regimen failed to improve overall survival (Figure 3)[44]. Maintenance interferon-alfa therapy following induction regimen has not been proven to improve survival either[45, 46].

Fludarabine can also be used in patients with lymphoma with or without rituximab combination[47]. Fludarabine alone in previously treated MCL can induce temporary responses in a third of patients lasting between 4 to 8 months[48]. In newly diagnosed patients, fludarabine appears to be more active, inducing responses in 60% , half of which is complete response[49]. Combining fludarabine with idarubicin or cyclophosphamide may improve induction of complete responses[50, 51]. Fludarabine and cyclophosphamide

combination(FC) can induce a higher response rate of 63% in patients recurrent MCL[51]. Previously untreated patients have response rate up to 100% with a complete response rate of 70% and 28 months of progression free survival[51].

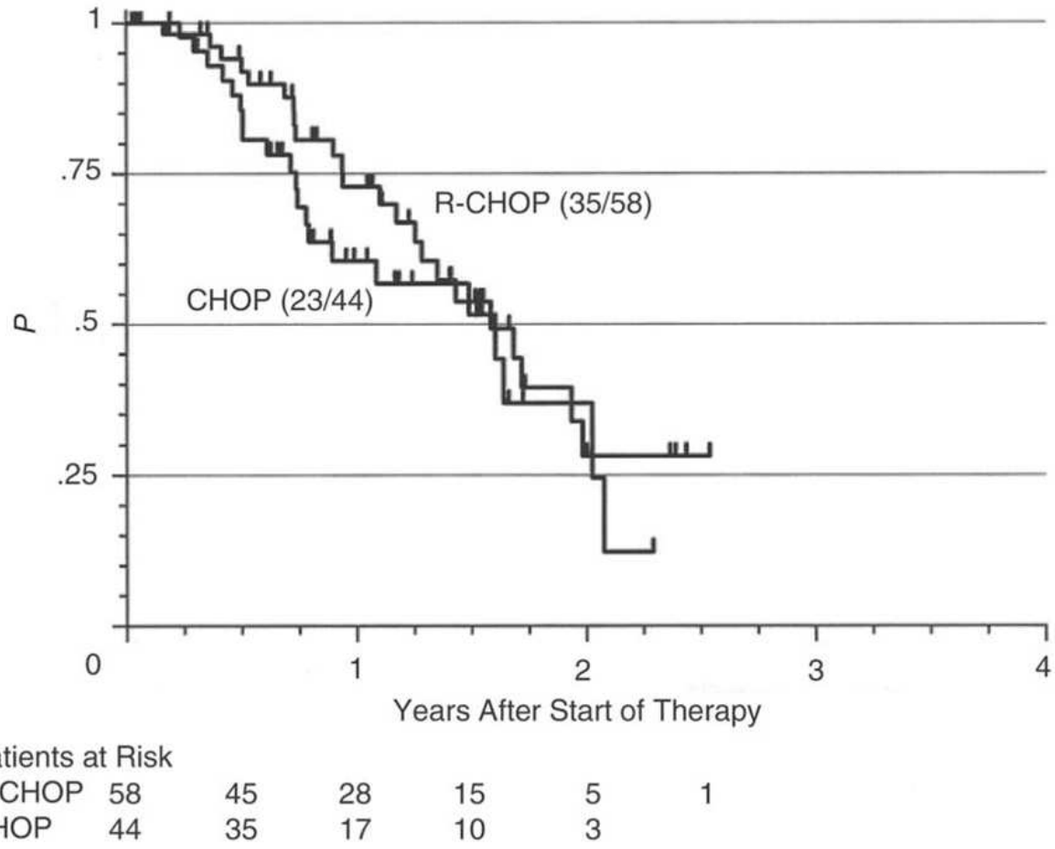

Fig. 3. Progression-free survival after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab and CHOP (R-CHOP)[44].

In a randomized study testing addition of rituximab to fludarabine, cyclophosphamide and mitoxantrone (FCM), patients in the rituximab arm were found to have significant improvement in disease free and overall survival[52-54]. Fludarabine combined with cyclophosphamide and rituximab is a highly effective regimen in patients relapsing from previously received CHOP regimen[55]. Addition of rituximab to the chemotherapy regimens does not appear to increase toxicity[56].

Although tolerating patients treated with the hyper-CVAD regimen had excellent response and survival rates of greater than 90% at 3 years and 4.6 years of time to treatment failure (TTF at 8yr , 16% if age>65, 46% if age<65) following 10 year observation period[7, 38, 57, 58], patients treated with conventional therapies have also reported to have similar 3 year survival rates[59, 60]. The hyper-CVAD regimen without stem cell transplantation was not associated with a plateau in the survival curves (Figure 4)[57]. In this study, beta-2-microglobulin levels and IPI/MIPI scores were found to predict survival[57]. Hyper-CVAD regimen data may suggest high efficacy of the high-dose Ara-C (HIDAC) regimen, which needs to be tested in further clinical trials.

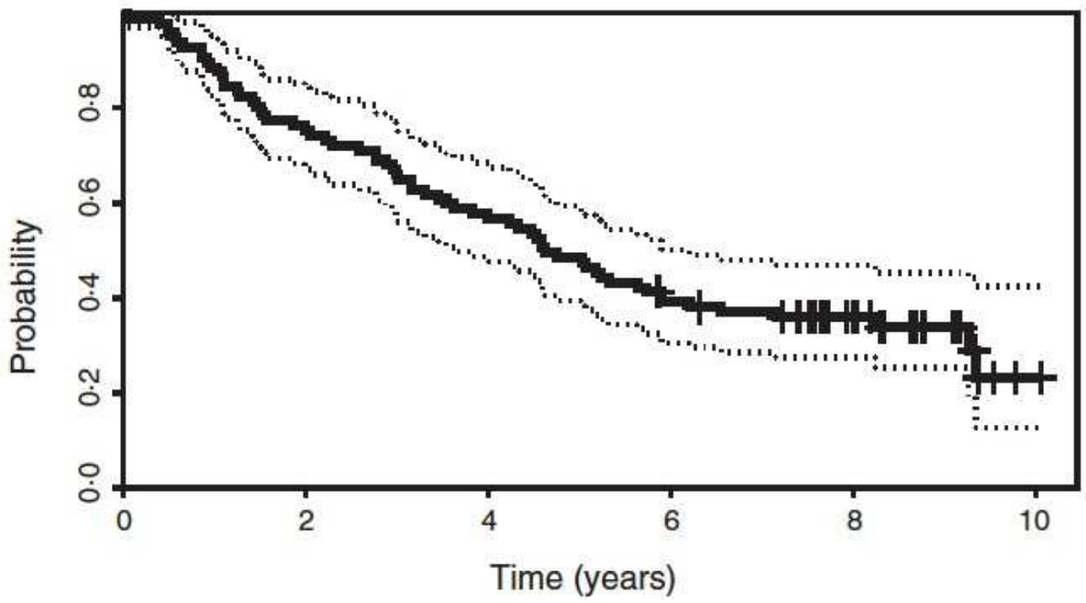

Fig. 4. Overall survival and time to failure in 97 patients treated with R hyper-CVAD alternating with R M/A[57].

Due to advanced age at the time of presentation of MCL, there is a concern about intensive therapy regimens being associated with higher toxicity rates requiring patient selection and patients tolerating intensive therapies are being selected for high-dose therapies with stem cell support.

5. New agents

Recently, bortezomib[61-63], lenalidomide[64-66], bendamustine[67-69], pixantrone[70], azaepothilone ixabepilone[71] and mTOR inhibitor temsirolimus[72-74] has been shown to demonstrate activity alone and in combination with rituximab and mitoxantrone, and may induce complete responses in relapsed or refractory MCL[61, 64, 69, 75, 76]. Along with rituximab, these biotherapy agents can be used frontline or may also be introduced into post transplant maintenance to prevent or treat relapses[61, 68, 77-81]. There may be an advantage of combining rituximab with bendamustine compared to combining with the conventional CHOP regimen in terms of disease free survival[82]. Recently, it was reported that frontline use of cladribine and rituximab can induce an overall response rate of 87%, with 61% of patients achieving complete remission, suggesting use of this combination for the initial treatment of MCL[83]. Radioimmunotherapy with ^{90}Y-labeled anti-CD20 monoclonal antibody (ibritumomab tiuxetan) or ^{131}I-rituximab is now being tested in phase I-II trials, including stem cell transplant setting[84-87].

6. High dose chemotherapy with autologous stem cell support (ASCT)

Since conventional and dose intense chemotherapy regimens have failed to induce cure or a plateau phase in time to treatment failure curves, high dose therapy with autologous stem cell support have been studied in the relapse setting[88] as well as consolidating complete responses following frontline chemotherapy regimens[88-94].

In a randomized trial testing ASCT versus IFN-alfa consolidation following response to CHOP or CHOP like regimens with or without rituximab, consolidation with BEAM/ASCT improved progression free survival (PFS) but has not been shown to improve overall survival (OS)(Figure 5)[93]. When patients responding to R-CHOP regimen received HIDAC therapy followed with autologous tranplantation with the BEAM regimen, also a plateau was not observed in time to treatment failure (TTF) and OS curves[94].

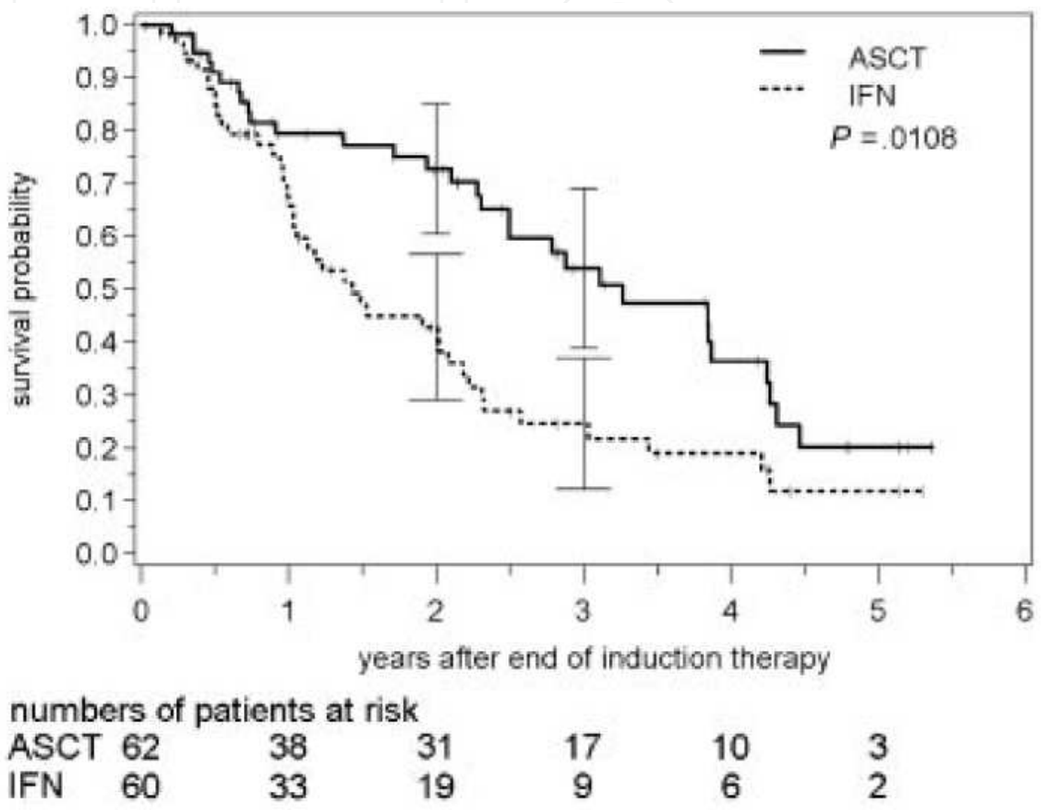

Fig. 5. Progression-free survival after high-dose radiochemotherapy followed by ASCT and IFN-alfa maintenance in MCL[93].

Autologous transplantation with conventional conditioning regimens without in vivo purging induced a median survival of 47 months[88]. Analysis of this patient group did not reveal a plateau in the survival curve[88].

Addition of rituximab to ASCT regimen leads to better event free survival (EFS) curves in patients with first remission, not affecting progression in patients with relapsed/refractory disease[91].

The R-HDS regimen consisting of high-dose sequential chemotherapy (including intravenous administration of high-dose cyclophosphamide, high-dose cytarabine, high-dose melphalan, and high-dose mitoxantrone plus melphalan) and in vivo purging with rituximab resulted in OS and EFS rates at 54 months were 89% and 79%, respectively[96]. These results compare favorably with the 42% OS rate and the 18% EFS rate observed in 35 age-matched historic controls treated with standard-dose chemotherapy at the participating centers (Figure 6)[96].

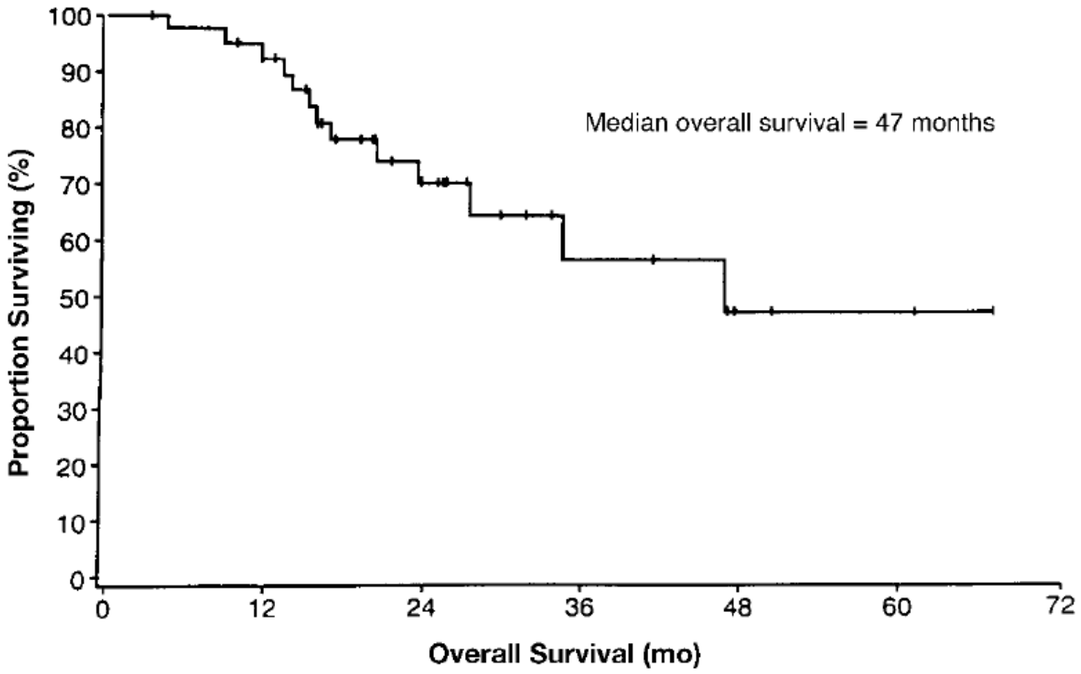

Fig. 6. Overall survival for mantle cell lymphoma patients after autologous transplantation without in vivo purging[88].

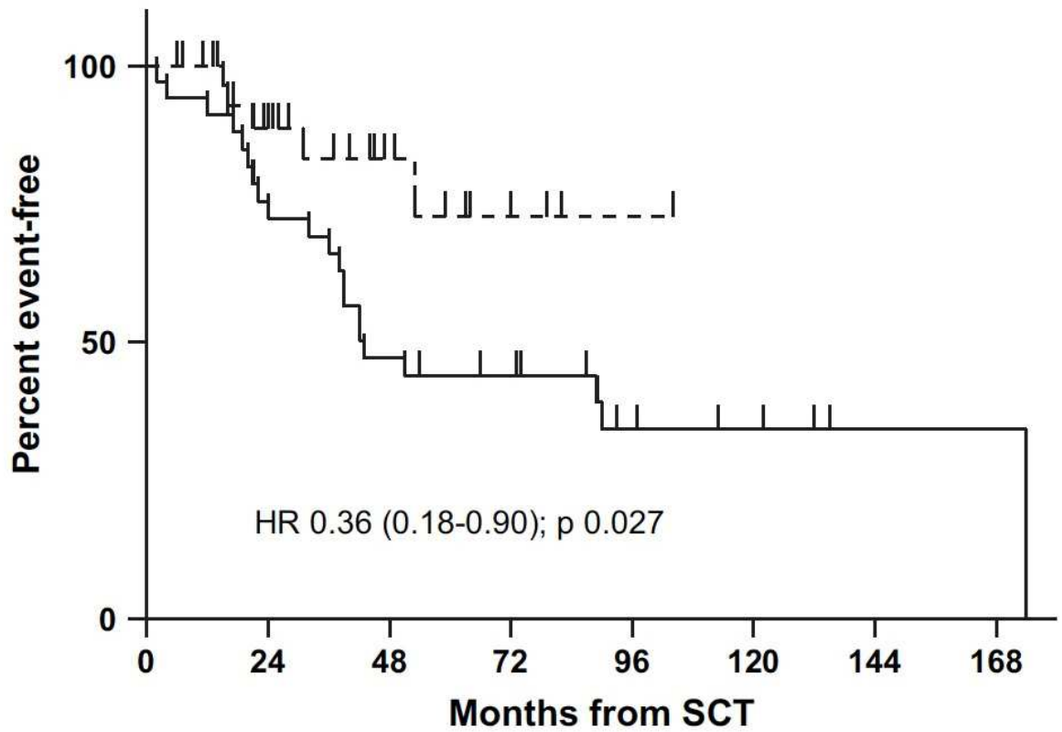

Fig. 7. EFS following ASCT after myeloablative therapy with (broken line) or without peritransplant rituximab (solid line)[95].

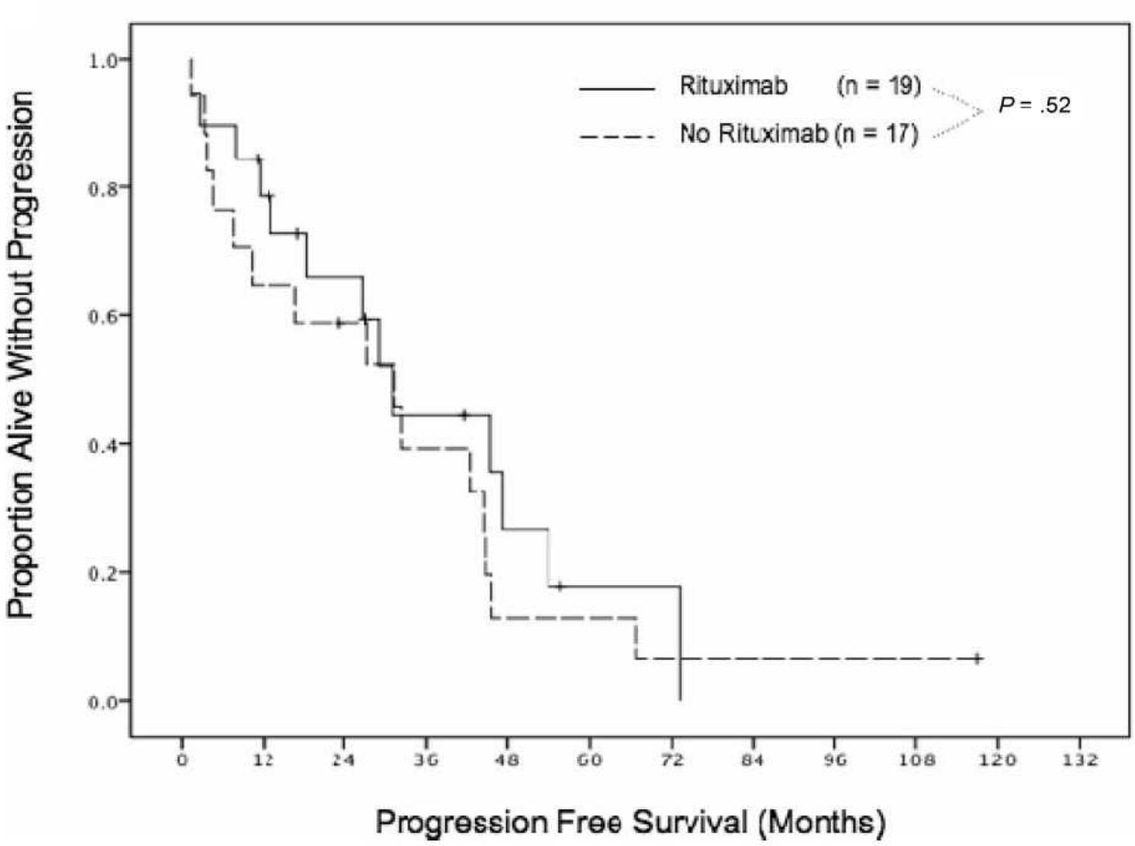

Fig. 8. PFS for patients receiving ASCT for relapsed/refractory disease[91].

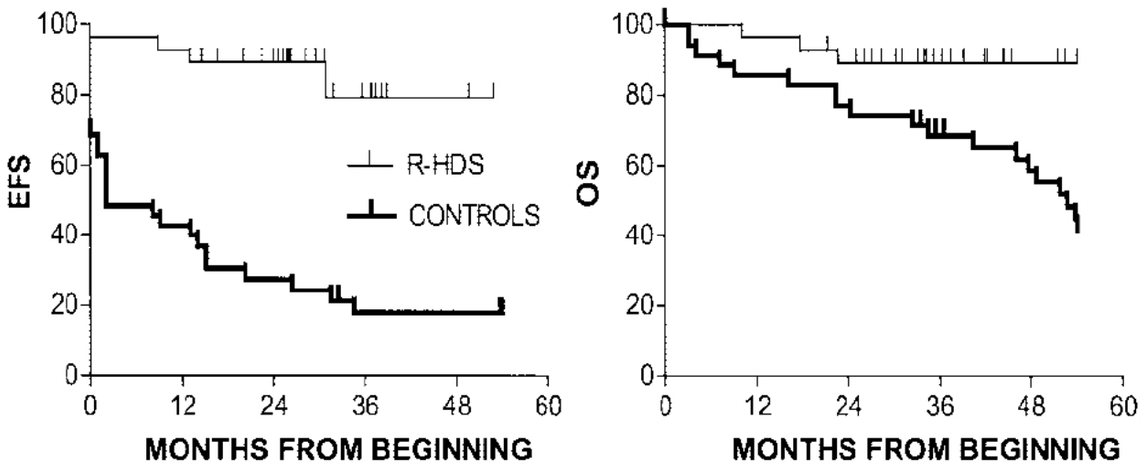

Fig. 9. Overall survival and event-free survival of patients treated with R-HDS versus conventional chemotherapy[96].

Heavily treated patients with multiple recurrences may undergo an effective salvage with high-dose radioimmunotherapy (RIT) coupled with autologous stem cell support[97].

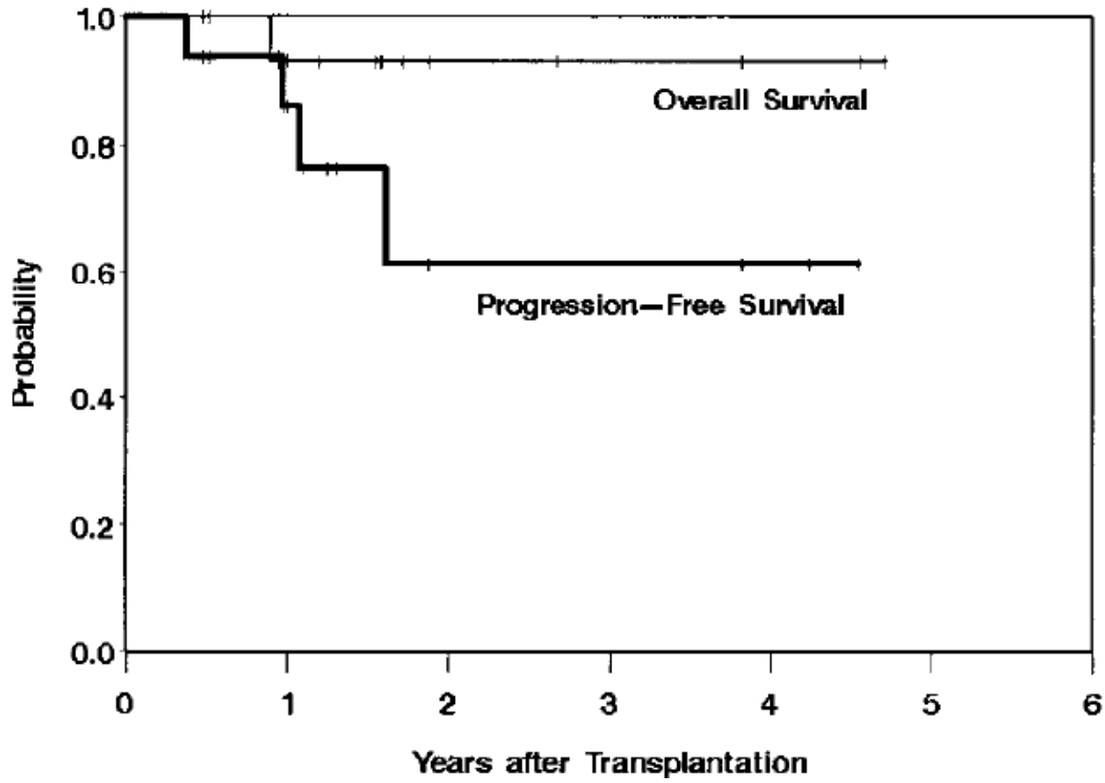

Fig. 10. OS and PFS obtained in patients with relapsed MCL treated with ^{131}I-tositumomab, etoposide, cyclophosphamide, and ASCT[97].

7. Allogeneic transplantation for achieving cure

Myeloablative or non-myeloablative allo-HSCT is generally performed in patients with lymphoma relapsing following auto-HSCT, since patients need tumor-free grafts that can induce a graft-versus-lymphoma (GVL) effect.

Physicians should consider the need for an allogeneic transplant when there is a need for a GVL effect (high risk of relapse) which can be predicted by the presence of;

- A high MIPI score
- Aggressive clinical behavior characterized by not achieving a satisfactory response to chemotherapy regimens
- remaining PET positive following ASCT[98]
- Multiple relapses

and;

- If the patient is young (<55 years) or,
- Autologous stem cells cannot be mobilized

in patients considered to be eligible following pretransplant screening tests.

Evidence for presence of graft versus lymphoma (GVL) effect has been reported in patients with MCL who underwent allo-HSCT[99]. CVL effect may be observed as conversion to pcr negativity for t(11;14) or achieving CR in the presence of GVHD[99], or observing lower relapse rates in allo-HSCT recipients compared to patients undergoing autologous

transplantation[100-102]. A healthy comparison of autologous and allogeneic transplants cannot be made at present, due to lack of randomized trials and the different prognostic groups undergoing each transplant type. By using myeloablative regimens for relapsed patients, allogeneic transplants can induce three year event free survivals (EFS)around 50%[99, 101-104]. However, if performed in first CR or PR, EFS induced by allo transplants at three years can be as high as 70%[103].

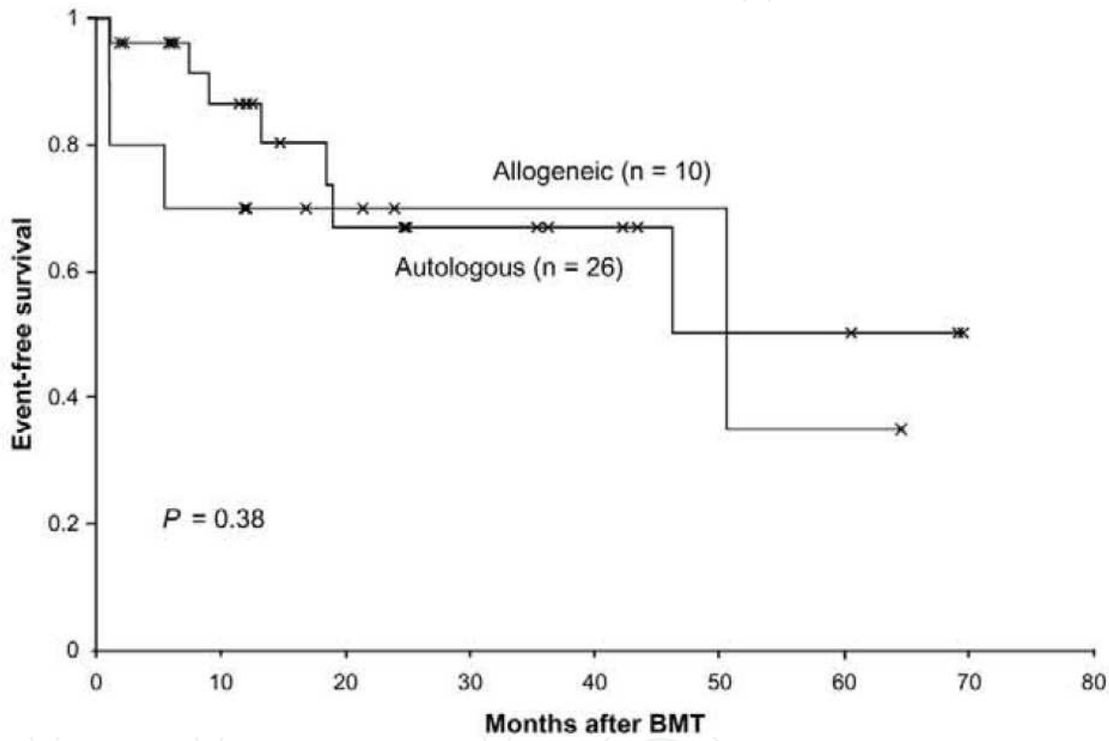

Fig. 11. Event-free survival according to type of BMT[103].

8. Reduced intensity allogeneic stem cell transplantation

In the allogeneic transplant setting, benefit of cure over transplant related mortality can be positively affected by using reduced intensity (RIC) or non-myeloablative (NMA) conditioning regimens[105-116]. Using donor lymphocyte infusions for GVL effect in patients undergoing allogeneic transplantation with RIC or NMA regimens, low transplant mortality rates (<10%) and higher OS (73 to 85%) and EFS rates (73 to 82%) can be achieved[105, 117, 118].

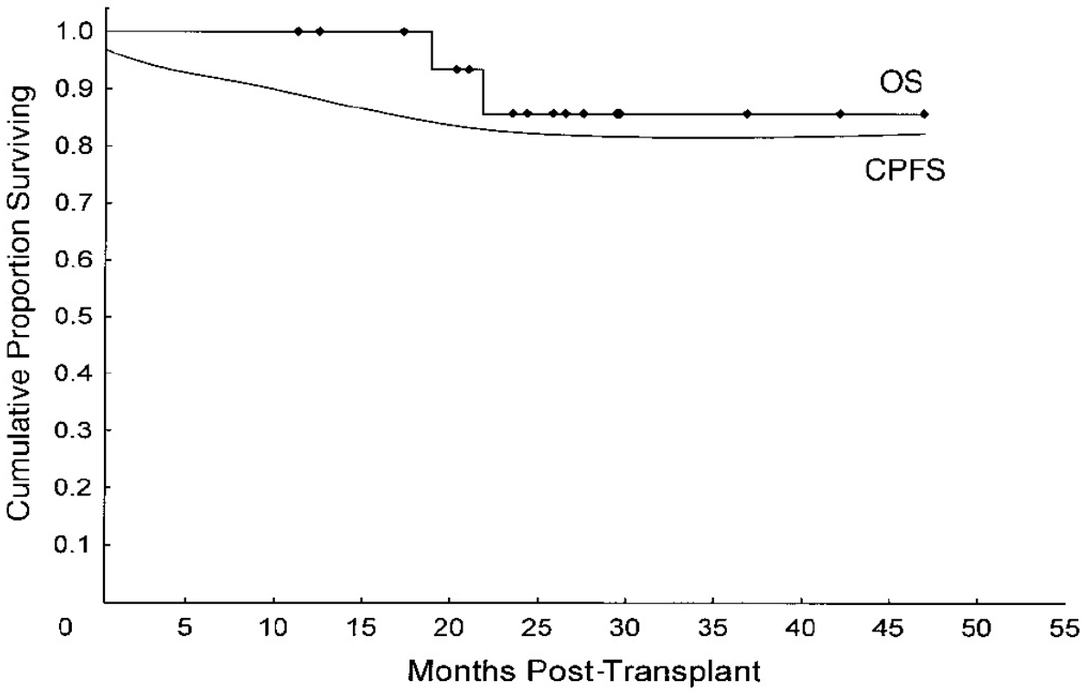

Fig. 12. Kaplan-Meier overall survival (OS) and current progression-free survival (CPFS) accounting for salvage post-DLI in with relapsed MCL who received NMA allogeneic transplantation[105].

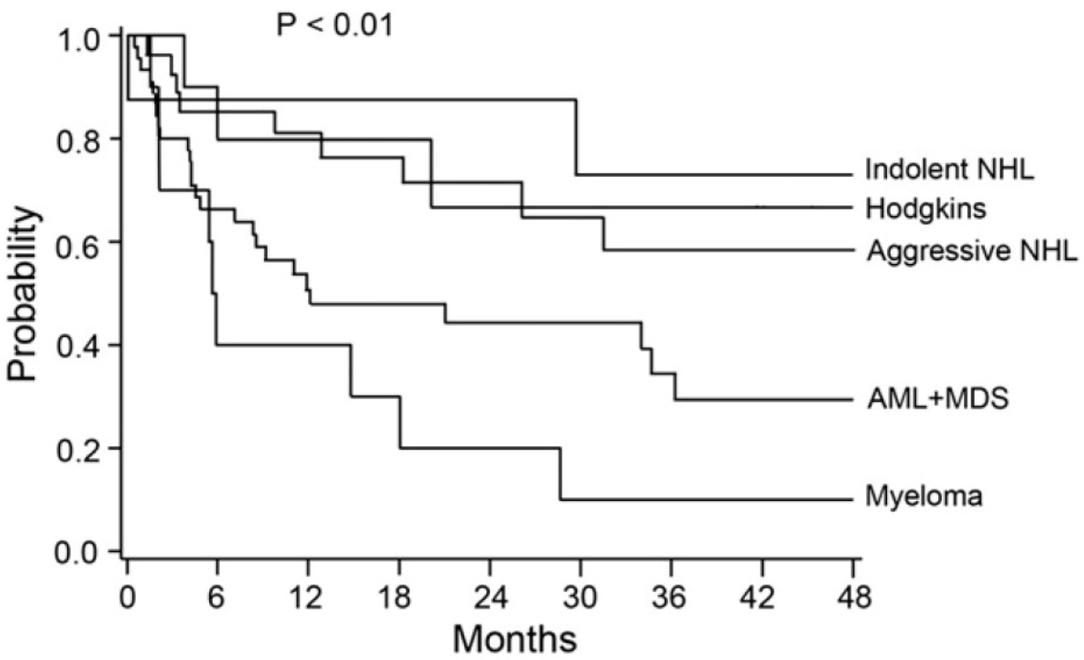

Fig. 13. Favorable overall survival following reduced intensity allogeneneic transplants by disease group[117].

9. Decision making for transplant options

While standard chemotherapy regimens do not offer long term progression free survival, intensive therapy followed by ASCT should be considered for each newly diagnosed patient[92], especially if the MIPI score is translating into poor prognosis.

Multiply relapsed patients will not do well after autologous transplants[91, 103]. Best time to perform an autologous transplant is following CR[91, 92, 119, 120] obtained after high-dose therapy with hyperCVAD or HDS regimen, coupled with rituximab[91], including in vivo purging prior to stem cell collection[81, 92, 96]. With this approach, patients eligible for these sequential intensive regimens may enjoy long term disease free survival, although cure cannot be achieved[121].

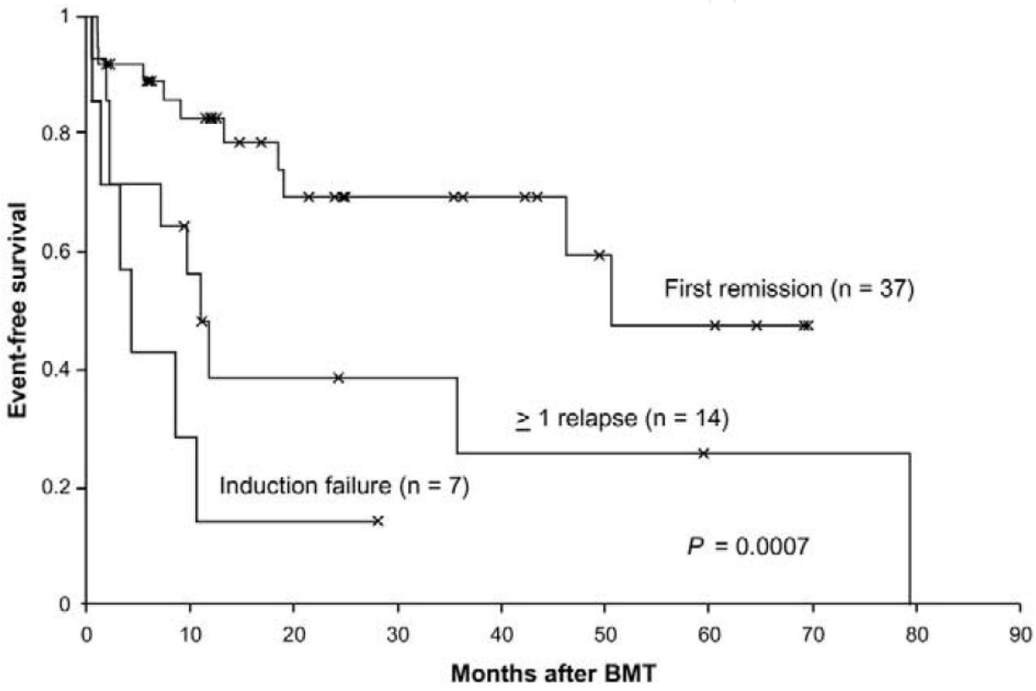

Fig. 14. Event-free survival according to remission status at BMT[103].

Newly diagnosed and relatively younger patients less than 60 years of age who are not eligible for ASCT or relapsing after ASCT, or patients with recurrence following chemotherapy, can still be cured by allogeneic SCT following an effective salvage regimen inducing CR or near CR[121].

As the outcome of transplantation is most promising in the newly diagnosed patients without chemorefractory disease, graft contamination and the lack of a survival plateau following autologous transplantation, allogeneic transplantation deserve investigation as the upfront therapy in the management of patients with MCL[92].

Patients over age 65, and individuals who are not eligible for ASCT with poor prognostic MIPI scores remain as a major challenge for the hematologist. In this group of patients, promising new drugs such as bendamustine, cladribine and bortezomib in combination with synergizing agents such as rituximab, may be offered to patients in the context of clinical trials. One should remember that ASCT with intermediate dose melphalan at doses

between 100 to 140 mg/m^2 can still be utilized in patients over age 65, as well as non-myeloablative allogeneic stem cell transplants, immediately after achieving a clinical complete response in experienced transplant centers. These approaches have to be tested in clinical trials in the near future.

10. Rational approaches in managing patients with MCL

Due to heterogeneity of disease, paucity of randomized trials, availability of a wide range of chemotherapy regimens including new agents, and altering prognostic factors among patients, an individualized treatment approach should be adapted for each patient diagnosed with MCL. As in therapy of patients with myeloma, long term survival may be achieved following sequential and risk-adapted use of available therapies such as intensive or nucleoside analogue based chemotherapy, followed by autologous and/or reduced intensity allogeneic transplantation, including radioimmunotherapy.

Rational strategy at present can be outlined as;

1. After assessing the MIPI score, low risk patients can be followed without transplantation strategy, because of late age of onset, which is over 60 in most patients. This group of patients will do well with standard chemotherapy regimens utilized in NHLs, such as R-CHOP or new generation combination regimens including a purine analogue and rituximab, such as R-FCM or FCR.
2. Due to its poor prognosis and failure to achieve improved survival curves with conventional chemotherapy regimens, consideration should be given to upfront autologous transplantation in patients with high MIPI scores. To induce remission FCR, R-hyperCVAD and R-CHOP-14 regimens seem to be effective approaches. Inducing high quality complete responses -molecular remission for t(11;14) translocation- prior to autologous transplantation may further improve disease free and overall survival curves. Success of this strategy has been shown in comparison to historical controls, and also has to be proven in randomized clinical trials.
3. Young patients with intermediate MIPI scores may choose to continue with the same approach with the ones with high scores as described above. Elderly patients may receive R-CHOP, R-FCM or FCR as the initial therapy.
4. Patients having recurrence following conventional chemotherapy or an autologous transplant and who are determined to be fit for an allogeneic transplant following a careful evaluation and screening tests should be given a chance to have this treatment option to achieve cure.
5. Regardless of the MIPI score, patients who are not eligible for high dose therapy and autologous stem cell support and relapsing after conventional chemotherapy regimens and not a candidate for an allogeneic transplant may be treated with bendamustine and cladribine containing regimens in the context of clinical trials.

Transplant strategy can be summarized as;

Patients with predicted poor survival by MIPI score should undergo intensive induction regimens if eligible, to achieve CR, followed by ASCT preferably in first remission. If cure is targeted, especially in young patients, allogeneic SCT may be performed following an excellent cytoreduction with ASCT or intensive chemotherapy regimen including high dose Ara-C and rituximab, such as R-HDS or hyper-CVAD regimens.

11. Emerging new drugs to improve results in the near future

New agents which may have potential to improve outcome of relapsed or refractory patients with MCL include chemicals targeting cyclin D1 and the cell cycle regulatory proteins (cdk), inhibitors of mammalian target of rapamycin, the proteasome, and proapoptotic family members[122].

Both histone deacetylase (HDAC) and mTOR inhibitors may downregulate cyclin D1 reducing cell cycle drive, which is upregulated in patients with MCL. Cyclin D1 is the key factor for upregulating cellular proliferation rate[22]. HDAC inhibitor sueroylanilide hydroxamic acid (vorinostat) has ability to reduce intracellular cyclin D1 levels in MCL cells, leading to inhibition of progression to S-phase in the cell cycle, and may induce response in MCL patients, currently being tested in phase I clinical trials[123]. Cyclin D1 protein itself can be used as a target for sensitized T-cells, generating a potential treatment option by cellular therapy[124].

Other than overexpression of cyclin D1, activation of mammalian target of rapamycin (mTOR) also plays a major role in growth and proliferation in MCL cells[125]. Inhibitiors of mTOR (rapamycin, temsirolimus, everolimus) may increase apoptosis and decrease proliferation rate by causing G1 arrest in the cell cycle[126]. Single agent temsirolimus has been shown to have clinical activity in phase II trials, and a randomized phase III trial[127-129]. Alternative mTOR inhibitor everolimus is currently in phase II trials[130, 131].

Deficiencies of Noxa and Bim proteins and aberrant expression of Bcl-2 may reduce apoptosis and lead to increased resistance to chemotherapeutic agents[132]. Proteasome inhibitors such as bortezomib and flavopiridol may function as accumulating cdk inhibitors (p21/p27), causing cell cycle arrest in malignant cells[132-134]. Accumulation of proapoptotic Noxa protein has been consistently shown in MCL cells treated with bortezomib[135].

There is a rationale combining bortezomib with HDAC inhibitor vorinostat. Vorinostat may be able to turn off cyclin D1, whereas bortezomib turns on cdk inhibitors p27 and p21, targeting two complementary genetic lesions involved in the cell cycle aberration in MCL cells which may lead to induction of apoptosis[136]. Bortezomib may also be combined with cyproheptadine, recently identified inhibitor of cyclin D1, synergistic in inducing apoptosis in vitro[137].

Development of new drugs for MCL will further improve the recent achievements in the management options published in the last decade, in a disease currently not curable by medical therapy except allogeneic transplantation.

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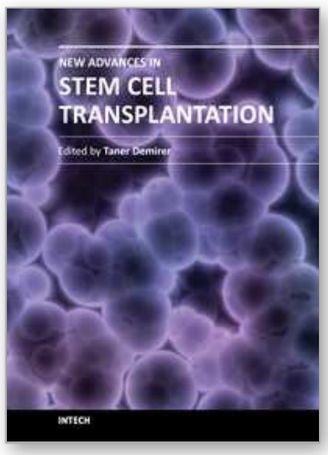

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This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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