HOW I TREAT MANTLE CELL LYMPHOMA

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Abstract

Mantle cell lymphoma (MCL) is included in the WHO classification as distinct lymphoma subtype characterized by the t(11;14)(q13;q32) translocation, which results in over-expression of Cyclin D1. The clinical presentation often includes extra-nodal involvement, particularly of the bone marrow and gut. The prognosis of patients with MCL (median OS 3-5 years) is the poorest among B cell lymphoma patients, even though a prospectively difficult to identify sub-group can survive for years with little or no treatment. Conventional chemotherapy is not curative but obtains frequent remissions (60-90%) which are usually shorter (1-2 years) compared to other lymphoma entities. Very intensive regimens, comprising autologous and allogeneic stem cell transplantation seem required to improve the outcome but, the median age of diagnosis being 60 years or more, such approaches are feasible only in a limited proportion of patients. The possibility to treat patients based on prognostic factors needs to be investigated prospectively.
**Diagnosis and staging**

The lymphoma nowadays included in the WHO classification with the name 'mantle cell lymphoma' (MCL) was first described by K. Lennert more than 30 years ago, and subsequently defined 'centrocytic lymphoma' in the Kiel-classification, but MCL was finally accepted as a separate entity only in the early 1990s, when it became evident that the t(11;14)(q13;q32) translocation was consistently present.

**Histological diagnosis**

The term MCL derives from the growth pattern of this lymphoma in its early stages, with neoplastic cells surrounding residual reactive germinal centres and replacing the normal follicle mantle (mantle zone pattern). At more advanced stages of tumour infiltration, MCL cells in the lymph nodes may show a vaguely nodular, or a diffuse growth pattern.

The classical cytological appearance of MCL is a monomorphic proliferation of small- to medium-sized lymphoid cells with irregular nuclear contours and inconspicuous nucleoli. Four cytological variants of MCL can be recognized, including the small cell variant, the marginal zone-like variant, the blastoid variant and the pleomorphic variant. The blastoid and pleomorphic variants are considered to be associated with a poorer prognosis.

The histological diagnosis can be difficult and immunophenotyping is usually required (Table 1). MCL cells express mature B-cell markers and IgM and/or IgD surface immunoglobulins. They are usually expressing CD5 but are negative for CD10 and BCL6. BCL2 protein is usually expressed and Cyclin D1 expression, which is ectopically expressed due to the presence of the t(11;14)(q13;q32) translocation, can be shown in nearly all cases (including the very infrequent cases with aberrant CD5-negative phenotype). However, the immunohistochemistry efficiency in determining cyclin D1 overexpression could be hampered by the quality of available material. Thus, fluorescence in situ hybridization (FISH) (Figure 1) is the technique of choice to demonstrate the presence of the translocation t(11;14). Polymerase chain reaction (PCR) with primers directed to the breakpoint regions on 11q13 and 14q32 has a high false negative rate (40–60%), when positive however, it is an excellent tool for molecular follow-up studies. These can be useful for the evaluation of the activity of...
new drugs or treatment strategies, while in clinical practice we abandoned this analysis, being expensive, time-consuming and not useful for clinical decisions.

**Molecular pathogenesis**

The genetic hallmark of MCL is the t(11;14)(q13;q32) that fuses the immunoglobulin heavy chain enhancer-promoter to the transcription unit of the proto-oncogene CCND1, encoding Cyclin D1. The translocation determines the ectopic and deregulated expression of cyclin D1, which is considered the primary molecular event in the pathogenesis of MCL, but additional oncogenic events are involved in MCL tumour progression. Comparative genomic hybridization and array based genomic studies have shown a variety of altered chromosomal regions in MCL, with genomic losses containing the loci of tumour suppressor genes (including ATM, CDKN2A, TP53) and gains involving oncogenes (e.g., MYC, SYK, BCL2). The presence of ataxia-telangiectasia mutated (ATM) or cell cycle checkpoint kinase 2 (CHK2) inactivating mutations in the germline of some MCL patients suggests that they can be implicated in development of the tumour and a model of multistep clinicopathological and molecular pathogenesis and progression has been proposed (Figure 2).

A pronounced cell cycle deregulation and the activation of abnormal pathways offer a number of possible therapeutic targets.

**Clinical Features**

In western countries MCL accounts for about 3% to 10% of all cases of non-Hodgkin lymphoma, with a striking predominance of the male gender (about 2:1 or greater in all series). The patients have a median age of 60 to 65 years and typically present with generalised non bulky lymphadenopathy. Most cases are diagnosed at advanced Ann Arbor stage and extra-nodal involvement is very frequent. Most common extra-nodal sites include bone marrow, liver, spleen, the Waldeyer ring and the gastrointestinal tract; this latter often with the appearance of a multiple lymphomatous polyposis of the intestine. A clearly leukaemic blood picture is not uncommon and some degree of peripheral blood involvement can be detected in nearly all the cases by flow cytometry. Skin involvement is usually a manifestation of disseminated disease, and is often associated with blastoid cytologic features. Symptomatic involvement of the central nervous system (CNS) is exceedingly rare at presentation but relapses in the
CNS have been reported in 4% to 22% in retrospective series\textsuperscript{15}, more frequently in patients with blastoid histology\textsuperscript{16} and in the very rare subset of Cyclin D1-negative MCL\textsuperscript{17}.

The clinical course is often indolent or moderately aggressive at diagnosis, with few or no symptoms and a good performance status, but with time the disease invariably become clinically aggressive and chemotherapy refractory, showing the worst long-term survival among all B-cell lymphoma subtypes\textsuperscript{18} (Figure 3). The median survival in most published series was in the range of 3 years in the past decades and has been reported to have risen to 5 years in most recent times\textsuperscript{19}. However, a subset of patients may show prolonged indolent behaviour and a longer survival. Unfortunately, there are no reliable tools to prospectively identify these cases.

**Prognostic factors**

The choice of the best treatment for each individual patient and the proper evaluation of the novel therapeutic options requires the possibility of stratifying the patients according their individual risk of relapse and death. Gene expression analysis profiles identified a cohort of twenty “proliferation signature” genes that predicts patient survival\textsuperscript{20} but this approach cannot be applied in daily practice. A PCR-based surrogate method based on a five gene model and which can as well be applied on paraffin embedded tissue has been recently proposed\textsuperscript{21} but it still needs proper validation. In addition to the common lymphoma indicators of prognosis (extranodal involvement, stage, age, PS, LDH), the ki67 proliferation index seems the most powerful predictor of survival in MCL also in the rituximab era\textsuperscript{5,22}. A blastoid morphology has often been associated with poorer outcome\textsuperscript{23}, while the influence of the growth pattern on survival is less clear\textsuperscript{24-26}. The utility of the IPI (international prognostic index) is controversial but recently a specific MCL prognostic score (MIPI) has been proposed\textsuperscript{27}. This score, based on the study of 455 patients only (the IPI and the FLIPI as a comparison are based on series of thousands of cases) identified four independent prognostic factors (age, performance status, LDH and leukocyte count) that can be used to stratify patients into three risk groups with an OS of approximately 2 (high risk), 4 (intermediate) and 6 years (low risk).

Leukaemic presentation and splenomegaly have been considered adverse prognostic indicators\textsuperscript{28}, however recent data suggests that if associated with the lack of nodal...
disease (especially if showing small cell variant morphology) they may indicate a subset of patients with particularly indolent behaviour.\textsuperscript{29,30}

All the above mentioned prognostic factors correlate with survival but none of them was validated as a tool for the selection of therapy.

**Staging procedures**

Standard staging procedures include routine laboratory analysis, bone marrow examination as well as immunophenotyping by flow cytometry of bone marrow and peripheral blood, computed tomography scan of the chest, the abdomen and the pelvis. There is very limited information on the use of \([18F]\)fluorodeoxyglucose positron emission tomography (FDG-PET) in MCL\textsuperscript{31-33} hence, at present, the use of FDG-PET in MCL should still be considered as investigational.

Cerebro-spinal fluid (CSF) evaluation is not usually required at presentation for MCL patients with classic morphology, unless neurologic symptoms are present. However, careful CSF examination by cytology and flow cytometry should be considered in the initial staging of patients with the blastoid variant.\textsuperscript{16}

Gastrointestinal involvement is a common feature, which however may not necessarily be symptomatic at presentation and can therefore be easily missed if endoscopy studies are not performed. Gastrointestinal symptoms are present in approximately one quarter of patients but, when baseline endoscopy studies are performed, gastrointestinal tract involvement can be found in up to 80\% of cases, often in biopsies from macroscopically normal mucosa.\textsuperscript{34,35} Although not an essential examination, because of the modest impact on therapeutic decisions\textsuperscript{34}, we usually perform upper and lower endoscopy in all patients who are fit enough to tolerate it, with the purpose of better defining the indication to localised treatment in the rare patients with early stage disease and for the purpose of better documenting CR in patients included into clinical trials.

**Therapy**

There are few solid data on how to treat MCL. This surprising fact is due to the recent definition of the disease, its relatively low incidence and the lack, until very recently, of a reliable and specific prognostic score\textsuperscript{27} which can be used in comparing data from different trials. The approach to treatment is largely based on the common belief that...
the disease is aggressive, although a survival of 86% at 3 years and a median overall survival of 7 years was recently described in a non aggressively treated cohort. While planning treatment for a new patient with MCL, physicians face a number of open questions, which are addressed in the following sections.

**The best combination chemotherapy regimen**

The active regimens in MCL are the same which are used for other lymphoma entities: alkylators based (COP/CVP), anthracycline based (CHOP), cladribine or fludarabine based (FC, FCM), or, more recently, bendamustine based (BOP) regimens, usually combined with rituximab. The data summarising the outcome of the chemotherapy regimens most commonly used in first line are presented in Table 2.

The majority of prospective data are available for CVP or CHOP-like regimens since fludarabine or cladribine based regimens were used only for patients not considered for autologous transplantation.

However, both the randomised study and the inter-study comparisons suggest that no combination is superior in terms of OS. Therefore the choice of the regimen depends chiefly on the overall goal, which the treating physician and the patient are aiming at. If an intensification with high-dose chemotherapy and PBSCT are planned and therefore a CR should be obtained, then a R-CHOP-like or even a more intensive regimen should be chosen. The CVAD regimen, including a continuous infusion of doxorubicin and hyper-fractionated cyclophosphamide showed excellent results, which were further enhanced by the addition of rituximab and bortezomib, although at the expense of more frequent and severe neuropathy.

**The role of cytarabine (Ara-C)**

As cytarabine was shown to be very active in the treatment of MCL, several investigators integrated it in first line regimens, either as part of classical salvage combinations like DHAP or at high-dose as used in the treatment of acute leukaemia. As shown in table 3, the addition of cytarabine improves the rate and quality of responses as well as their duration, but at the expense of a higher toxicity: approximately 5% toxic deaths, 15% severe infections, 30% severe thrombocytopenia. This option is therefore applicable only for younger patients preparing for autologous transplantation and treated in referral centres.
Transplantation: when and how

Intense chemotherapy results in a high proportion of responses and complete responses, but these are usually of shorter duration than in other lymphoma types. To enhance these results and with the hope of some cures, younger patients are generally consolidated with high-dose chemotherapy and PBSCT. Data of cohorts undergoing intensive induction followed by PBSCT consolidation suggest indeed a higher EFS and possibly OS compared to historical controls (Table 4), but the only randomised study did not as yet reach conclusive results. All data suggest that there is no disease-free plateau and therefore probably all patients will eventually relapse. An exception is represented by the recently published Nordic trial including 160 patients treated with R-maxi-CHOP alternating with HD-Ara-C and consolidation with BEAM or BEAC supported by in-vivo R-purged autologous stem cells. In this study with a median observation of 4 years, a 6-years EFS of 56% was observed with no patient relapsing after 5 years. Similar data are seen for 63 patients transplanted in CR and included in BMT registries.

As in other indolent lymphomas, allogeneic BMT is the only potentially curative treatment for advanced disease, but its application is limited by the important age-dependent mortality. Even with non-myeloablative conditioning, the TRM in registry data was 50% and the OS 30% at 2 years, although some centres of excellence present more encouraging data. The evidence of a GvLy effect in MCL is weaker than for follicular lymphoma and registry data of transplanted MCL do not clearly show a plateau suggesting cure, although a few relapsed patients experienced very long remissions.

Rituximab in MCL

In MCL Rituximab has a somehow less impressive activity than in other B-cell indolent malignancies. The response rate in both untreated and pre-treated patients is approximately 30% and the median duration of response 6 months. When combined with chemotherapy it improves the CR rate and a comprehensive systematic review and meta-analysis of seven randomized controlled trials indicated that rituximab plus chemotherapy may be superior to chemotherapy alone with respect to overall survival in MCL (HR for mortality = 0.60; 95% CI = 0.37 to 0.98). In this meta-analysis, however, there was a strong heterogeneity among the trials, making this...
survival benefit not completely reliable\textsuperscript{69}. Used as maintenance after either single agent rituximab, chemotherapy or chemo-immunotherapy induction, rituximab marginally improves EFS but has no effect on OS \textsuperscript{66,70}.

The role of radiotherapy

As MCL usually presents at an advanced stage, systemic treatment is the standard, and no much data are available on the activity of radiotherapy. Two retrospective studies suggest that radiotherapy is active in MCL, both alone or added to chemotherapy \textsuperscript{71,72}. The belief of European cooperative groups that TBI regimens are more appropriate than chemotherapy as conditioning regimens before PBSCT in MCL is based on weak evidence \textsuperscript{73} and has been questioned more recently.

The recently available radio-immuno-therapy (RIT) is an elegant technique to deliver radiotherapy in a targeted fashion. Anti-CD20 antibodies combined with a radioactive isotope (Yttrium-90 or Iodine-111) have activity in a number of lymphomas, including MCL. When RIT was used to consolidate remissions after (immuno)-chemotherapy, it resulted in improvement of percentage, quality and duration of responses compared to historical controls\textsuperscript{74}. RIT was also used (either at standard or at high-dose) to improve on the activity of high-dose chemotherapy in the setting of autologous stem cell transplantation, showing feasibility and suggesting a possible benefit. \textsuperscript{75,76}

New drugs active in MCL

Several new drugs have shown a remarkable single agent activity in relapsed or resistant MCL and many, mainly of the so called “molecular targeted” type, are now under investigation. Of those clinically available, the more consistent response rates are 33% for bortezomib \textsuperscript{77}, 41-53% for lenalidomide \textsuperscript{78,79} and 22-41% for temsirolimus. \textsuperscript{80-82} These compounds and others are now investigated in clinical trials for their possible role in combination with other agents active in MCL. The combination of thalidomide with rituximab \textsuperscript{83} showed remarkable activity in a small group of 16 elderly patients with relapsed disease (RR 81%) and the combination of bendamustine with rituximab obtained astonishingly high RR and CR rates (75-92% and 42-50% respectively). \textsuperscript{45,84}
Suggested treatment algorithm

MCL is generally a systemic disease, but a small proportion of cases (10-20%) is diagnosed with only 1-3 adjacent involved LN sites. In these cases, in analogy with the common practice for other lymphoma types, we treat these patients with involved field radiotherapy, preceded by 3-4 cycles of chemotherapy for patients who are young and fit enough for it. This strategy obtained long term remissions in 11 out of 16 patients treated in British Columbia 71.

For advanced disease, considering the biological characteristics and the treatment options illustrated above, the issue is if MCL should be approached as done in DLBCL (with which it shares the aggressive biology), i.e. R-CHOP-like treatment to everybody, or rather with an approach as in FL (with which it shares the characteristic of non curability), i.e. tailored treatment based on prognostic factors and clinical characteristics of the patient.

Even though immediate combination chemotherapy for those who can tolerate it, has been the far most used approach in the last decades, a watch and wait policy could be advocated, as we know that a fraction of patients present with a rather indolent form of MCL. Investigators at the Weill Cornell Medical College recently reported on 31 asymptomatic MCL patients with median age 58, who were approached by observation and treated only when clinically needed (all intervals >3 months). Fourteen of these remained without treatment for > 1 year and the OS of this group was similar to an institutional comparison group (n=66) who was treated immediately at diagnosis. 85 This is an interesting observation, however it must be noted that it comes from a retrospective analysis of a small group of cases and to extrapolate that a watch and wait policy could be advocated for a selected subgroup of MCL patients may be premature.

Therefore, because MCL is to be considered a generally aggressive disease, and because none of the biological and clinical prognostic factors have been validated as tools for the selection of therapy, our practice is to start therapy at diagnosis, while tailoring treatment to the age and the general condition of the patient.
First line treatment

Treatment of the young and fit

In several B-cell lymphomas, as FL or DLBCL, the advent of rituximab improved patient prognosis and changed the treatment approach, reducing the role of more aggressive treatment in front line. In MCL in contrast, the outlook of patients has not changed significantly and we are still facing an aggressive disease with a generally dismal prognosis, a median survival of 5 years and a tendency to relapse early and to respond insufficiently to salvage treatment. The disease often involves the BM, so that if autologous transplantation is planned the collection of blood stem cells with the minimal amount of contaminating tumour should be performed as early as possible. For these reasons we apply an aggressive approach for patients who are young (<60-65 years) and fit (no relevant co-morbidity). In these cases the clinical presentation of the disease (whether involving mainly the lymph nodes, the bone marrow and spleen or the gut) is not relevant for the choice of therapy. In our institution we decided to use the R-hyperCVAD/R-HD-MTX-Ara-C regimen for 4-6 cycles, followed by a consolidation with BEAM and PBSCT. Even though this approach was not confirmed as optimal in randomised trials, it appears to be very active and safe enough if applied in tertiary centres with sufficient expertise in high-dose therapy. Because the incidence of MCL patients with age < 65 is similar to that of AML cases of the same age, we believe that the suggestion to treat them all in tertiary centres with expertise in the treatment of acute leukemia should not be considered exaggerated.

Approach to the elderly and fit

Patients too old for autologous transplantation, but who are fit enough to receive intensive treatment should be given chemotherapy with rituximab. We have chosen to treat these cases with R-CHOP or R-CVP (depending on the cardiac co-morbidities), but regimens such as R-BOP or R-FCM have as well shown to be suitable for this purpose, and should be selected based on their side effect profile and the physician confidence with the regimen. Because of its toxicity profile, we do not add HD-Ara-C to these patients. On the other hand, it could be an option to consolidate these remissions with radio-immunotherapy, as it significantly improves the duration of remission without hampering the quality of life. Due to problems in obtaining payment of this expensive treatment by insurances, we are not routinely applying this option to our patients.
Treatment of the unfit

Patients who, either because of age or of co-morbidities, are unable to tolerate aggressive treatment, are treated with palliative chemotherapy of reduced intensity, usually with single agents. Of all the possible options, because of the favorable toxicity and cost profile, we often still choose to give oral chlorambucil, eventually combined with rituximab. The response rate and duration of this combination is satisfactory, as is the minimal impact on the quality of life.

Second line treatments

It has been proposed that the improvement in survival observed in the last decade is not due to better first line treatments but rather to improved second-, third- and fourth-line therapeutic options. Whether this is true or not, when patients relapse after an aggressive approach the goal of treatment becomes palliation of symptoms, and second line treatments with few side effects should be preferred. An exception is the relatively rare case of young and motivated patients with a compatible donor: here we consider the possibility of an allogeneic transplant and the pros and cons of such a procedure is discussed. If an allogeneic transplant is foreseen, we induce remission with a cis-platin based regimen (ESHAP) as done for other lymphomas.

A variety of treatments have shown a good therapeutic index at relapse. They comprise single agents as thalidomide, chlorambucil, bendamustine, cladribine, or newer agents such as bortezomib, lenalidomide or temsirolimus. Combination treatments like R-FC, R-FCM, gemcitabine/dexamethasone +/- cisplatin obtain a higher response rate but have probably no impact on survival and are at risk of causing major side effects. Low-dose metronomic PEP-C is a new combination of orally administered drugs which is both well tolerated and active.

In spite of the clinical activity of many compounds and regimens, the treatment outcome of relapsing mantle cell lymphoma patients who are not suitable for allogeneic transplantation remains dismal and no curative options are available. Therefore, we believe that whenever possible these patients should be offered the possibility of entering clinical trials testing new agents. When this is not possible, for practical reasons we usually try chlorambucil first, or CVP if a rapid response is needed for
symptom palliation. Bortezomib is our next choice, followed by lenalidomide, each of these eventually combined with rituximab.

Eventhough in some countries it is customary to add rituximab to any line of therapy for any B-cell neoplasia, we consider MCL as one of the lymphomas less sensitive to this antibody. We therefore do not add rituximab to subsequent treatments if progression occurred within 6 months form the termination of a previous R-containing therapy.

Finally radiotherapy, either in the form of irradiation of symptomatic localisations or in the form of radio-immunotherapy can be a good choice in selected patients. A problem with this latter form of treatment is that a BM infiltration < 25% and a normal platelet count are needed, both conditions which are not often met in relapsed MCL.

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Author Contributions

Both authors wrote the paper. There are no conflicts of interest to declare.
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<table>
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<tr>
<th>Histologic subtype</th>
<th>CD5</th>
<th>CD23</th>
<th>CD43</th>
<th>CD10</th>
<th>BCL6</th>
<th>Cyclin D1</th>
<th>slg</th>
<th>slg type</th>
<th>clg</th>
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<tr>
<td>Mantle cell Lymphoma</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>M ± D</td>
<td>–</td>
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<tr>
<td>Follicular Lymphoma</td>
<td>–</td>
<td>–/+</td>
<td>–</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>G ± M</td>
<td>–</td>
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<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>–</td>
<td>–</td>
<td>+</td>
<td>M ± D</td>
<td>–/+</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
<td>M</td>
<td>+</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>+</td>
<td>M</td>
<td>+/-</td>
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Mantle cell lymphoma differential diagnosis is not always straightforward and immunohistochemical studies are usually needed: the most typical immunophenotypic features of indolent mature B-cell neoplasms are summarised in the table (slg, surface immunoglobulin; clg, cytoplasmic immunoglobulin; +, >90% positive; +/-, >50% positive; +/-, <50% positive; -, <10% positive)
Table 2: Large (> 30 patients) prospective studies of combination regimens for MCL in first line

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>N</th>
<th>ORR</th>
<th>CRR</th>
<th>PFS/EFS</th>
<th>2y-OS</th>
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<tr>
<td>COP/CVP</td>
<td>Meusers, 1989(^{37})</td>
<td>37</td>
<td>84%</td>
<td>22%</td>
<td>10 mos</td>
<td>65%</td>
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<td></td>
<td>Teodorovic, 1995(^{40})</td>
<td>35</td>
<td>60%</td>
<td>40%</td>
<td>20 mos</td>
<td>45%</td>
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<tr>
<td></td>
<td>Unterhalt, 1996(^{41})</td>
<td>46</td>
<td>83%</td>
<td>18%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CHOP</td>
<td>Meusers, 1989(^{37})</td>
<td>26</td>
<td>88%</td>
<td>38%</td>
<td>7 mos</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Lenz, 2005(^{38})</td>
<td>60</td>
<td>75%</td>
<td>7%</td>
<td>19 mos</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>Nickenig, 2006(^{39})</td>
<td>46</td>
<td>87%</td>
<td>15%</td>
<td>21 mos</td>
<td>85%</td>
</tr>
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<td>MCP</td>
<td>Nickenig, 2006(^{39})</td>
<td>40</td>
<td>73%</td>
<td>20%</td>
<td>15 mos</td>
<td>85%</td>
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<tr>
<td></td>
<td>Herold, 2008(^{68})</td>
<td>46</td>
<td>63%</td>
<td>15%</td>
<td>13 mos</td>
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<td>R-MCP</td>
<td>Herold, 2008(^{68})</td>
<td>44</td>
<td>71%</td>
<td>32%</td>
<td>18 mos</td>
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<td>R-CHOP</td>
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<td>94%</td>
<td>34%</td>
<td>20 mos</td>
<td>76%</td>
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<tr>
<td></td>
<td>Howard, 2002(^{67})</td>
<td>40</td>
<td>96%</td>
<td>48%</td>
<td>17 mos</td>
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<td>VcR-CVAD</td>
<td>Kahl, 2008(^{47})</td>
<td>30</td>
<td>90%</td>
<td>77%</td>
<td>73%, at 18 mos</td>
<td>97%, at 18 mos</td>
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<td>Regimen</td>
<td>Reference</td>
<td>N</td>
<td>ORR</td>
<td>CRR</td>
<td>Toxicity</td>
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<tr>
<td>HyperCVAD/MTX-Ara-C</td>
<td>Khouri, 1998&lt;sup&gt;48&lt;/sup&gt;</td>
<td>45, 20 untreated</td>
<td>93%</td>
<td>38%</td>
<td>Thrombocytopenia 85%, Infections 10%</td>
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<tr>
<td>HyperCVAD/MTX-Ara-C</td>
<td>Romaguera, 2000&lt;sup&gt;92&lt;/sup&gt;</td>
<td>25, age &gt;65</td>
<td>92%</td>
<td>68%</td>
<td>Toxic death 8%, infections 5%</td>
<td></td>
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<tr>
<td>R-HyperCVAD/R-MTX-Ara-C</td>
<td>Romaguera, 2005&lt;sup&gt;51&lt;/sup&gt;</td>
<td>97</td>
<td>97%</td>
<td>87%</td>
<td>Toxic death 5%, MDS 3%</td>
<td></td>
</tr>
<tr>
<td>R-HyperCVAD/R-MTX-Ara-C</td>
<td>Epner, 2007&lt;sup&gt;52&lt;/sup&gt;</td>
<td>49</td>
<td>88%</td>
<td>58%</td>
<td>Toxic death 2%, hematotoxicity 87%</td>
<td></td>
</tr>
<tr>
<td>R-HyperCVAD/R-MTX-Ara-C</td>
<td>Merli, 2008&lt;sup&gt;53&lt;/sup&gt;</td>
<td>32</td>
<td>53%</td>
<td>50%</td>
<td>Toxic death 6%, severe infections 15%</td>
<td></td>
</tr>
<tr>
<td>R-DHAP</td>
<td>de Guibert, 2006&lt;sup&gt;56&lt;/sup&gt;</td>
<td>25</td>
<td>96%</td>
<td>92%</td>
<td>Thrombocytopenia 33%</td>
<td></td>
</tr>
<tr>
<td>CHOP x 3 + DHAP x 3</td>
<td>Lefrèvre, 2004&lt;sup&gt;50&lt;/sup&gt;</td>
<td>28</td>
<td>92%</td>
<td>84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP x 3 + R-DHAP x 3</td>
<td>Delarue, 2008&lt;sup&gt;54&lt;/sup&gt;</td>
<td>60</td>
<td>95%</td>
<td>61%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP x 3 + 1 x HD-Ara-C</td>
<td>Van't Veer, 2008&lt;sup&gt;55&lt;/sup&gt;</td>
<td>87</td>
<td>72%</td>
<td>29%</td>
<td>Infections 30%</td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>Reference</td>
<td>N</td>
<td>3y EFS</td>
<td>3y OS</td>
<td>Main Toxicity</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------------------</td>
<td>----</td>
<td>----------</td>
<td>----------</td>
<td>------------------------------------</td>
<td></td>
</tr>
<tr>
<td>HyperCVAD/HD-MTX-Ara-C</td>
<td>Khouri, 1998&lt;sup&gt;48&lt;/sup&gt;</td>
<td>25</td>
<td>72%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Khouri, 2003&lt;sup&gt;49&lt;/sup&gt;</td>
<td>31</td>
<td>43% at 5 yrs</td>
<td>77% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 x APO + Rituximab + sequential high-dose</td>
<td>Gianni, 2003&lt;sup&gt;93&lt;/sup&gt;</td>
<td>28</td>
<td>80%</td>
<td>90%</td>
<td>18% CMV reactivation</td>
<td></td>
</tr>
<tr>
<td>CHOP + HD-CVB + Rituximab</td>
<td>Mangel, 2004&lt;sup&gt;94&lt;/sup&gt;</td>
<td>20</td>
<td>89%</td>
<td>88%</td>
<td>Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>6xCHOP + HD-dexaBEAM</td>
<td>Dreyling, 2005&lt;sup&gt;57&lt;/sup&gt;</td>
<td>62</td>
<td>54%</td>
<td>83%</td>
<td>5% toxic deaths</td>
<td></td>
</tr>
<tr>
<td>CTAP/VMAC + HD-BuCy</td>
<td>Evens, 2007&lt;sup&gt;95&lt;/sup&gt;</td>
<td>25</td>
<td>50%</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP+HD-Ara-C +HD-R-Cy-TBI</td>
<td>Dreger, 2007&lt;sup&gt;96&lt;/sup&gt;</td>
<td>34</td>
<td>80%</td>
<td>100%</td>
<td>79% severe mucositis</td>
<td></td>
</tr>
<tr>
<td>R-maxiCHOP +R-HD-Ara-C+R-BEAM</td>
<td>Geisler, 2008&lt;sup&gt;58&lt;/sup&gt;</td>
<td>160</td>
<td>70%</td>
<td>85%</td>
<td>5% toxic deaths</td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1.**
FISH (Fluorescence in situ Hybridization) analysis on interphase (left panel) and metaphase nuclei (using the LSI® IGH/CCND1 XT Dual Color, Dual Fusion Translocation DNA Probe) identifying the presence of the t(11;14) (q13;q32) chromosomal translocation. One orange (CCND1 on chromosome 11q13), one green (IGH on chromosome 14q32) and two fusion signal pattern (der(11) and der (14), indicating the chromosomal rearrangements produced by the translocation) can be observed.

**Figure 2.**
Model of molecular pathogenesis and progression of MCL proposed by Jares, et al. Ataxia-telangiectasia mutated (ATM) or cell cycle checkpoint kinase 2 (CHK2) inactivating mutations have been found in the germline of some MCL patients and it has been suggested that these mutations may facilitate the lymphoma development. The t(11;14)(q13;q32) translocation occurs in an immature B cell and results in the ectopic and deregulated expression of cyclin D1, and early expansion of tumour B cells in the mantle zone areas of lymphoid follicles. This translocation is considered a primary pathogenetic event that deregulates the cell cycle control, probably by overcoming the suppressor effect of retinoblastoma 1 (RB1) and the cell cycle inhibitor p27. Acquired inactivation of DNA damage response pathways may then facilitate additional oncogenic events and the development of classical mantle cell lymphoma. Further genetic alterations may target genes of the cell cycle and survival regulatory pathways, leading to more proliferative and aggressive variants. *(Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer. Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat Rev Cancer 7: 750-62.2007, copyright 2007).*

**Figure 3.**
Cause-specific survival of the main B-cell lymphoma subtypes in the series of the Oncology Institute of Southern Switzerland, 1980-2006. (MZL, marginal zone lymphoma; FL, follicular lymphoma; DLCL, diffuse large cell lymphoma; MCL, mantle cell lymphoma).
Figure 1
Figure 2

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Germline
ATM
CHK2
mutations

Naive B-Cell

indolent clinical behavior → aggressive clinical behavior

Early MCL → Classical MCL → Blastoid MCL

in situ MCL
Mantle Zone Variant
Small Cell Variant
Classical MCL
Pleomorphic Variant
Blastoid Variant

additional genomic alterations with gains involving oncogenes and losses involving tumor suppressor genes

t(11;14)
Cyclin D1

ATM
CHK2

INK4A / CDK4 / RB1
ARF / MDM2 / p53

Complex karyotypes
High proliferation

RB1
p27
Figure 3
How I treat mantle cell lymphoma

Michele Ghielmini and Emanuele Zucca