Ann Hematol (2004) 83:71–77
DOI 10.1007/s00277-003-0774-2

REVIEW ARTICLE

G. Lenz · M. Dreyling · W. Hiddemann

Mantle cell lymphoma: established therapeutic options and future directions

Received: 13 August 2003 / Accepted: 20 August 2003 / Published online: 11 December 2003
© Springer-Verlag 2003

Abstract During the last few years, new insights into the biology of mantle cell lymphoma have been obtained. However, with a median survival of only 3 years, mantle cell lymphoma remains the lymphoma subtype with the poorest prognosis. At initial diagnosis most patients present with advanced Ann Arbor stage III or IV and conventional chemotherapy hardly alters the continuously declining survival curve. Recently, two prospective randomized studies of the German Low Grade Lymphoma Study Group (GLSG) clearly confirmed the superiority of a combined immunochemotherapy. In a randomized study of the European mantle cell lymphoma Network, consolidation with myeloablative radiochemotherapy followed by autologous stem cell transplantation improved the progression-free survival in patients younger than 65 years. However, relapses are still observed at a high frequency. Thus, new therapeutic strategies such as radioactively labeled antibodies or molecular targeting agents (e.g. Bortezomib or flavopiridol) are urgently warranted to further improve the clinical outcome of mantle cell lymphoma.

Keywords Mantle cell lymphoma · Review · Biology · Therapy · Prognosis

Introduction

Mantle cell lymphoma has been recognized as a distinct subentity of lymphoma in the recent WHO lymphoma classification [29]. With a median age of 65 years at diagnosis, it primarily represents a disorder of the male elderly. The incidence of mantle cell lymphoma is approximately 2–3/100,000/year [9, 25] representing approximately 5–10% of all lymphoma cases in North America and Europe [40, 60]. In contrast to other lymphoma subtypes, the etiology and molecular pathogenesis of mantle cell lymphoma remains unknown.

In recent years, important insights into the molecular biology of mantle cell lymphoma have been obtained. However, due to the aggressive clinical course of the disease, mantle cell lymphoma is still characterized by a poor prognosis with a median survival of only 3 years and only 10–15% long-term survivors. The purpose of this review is to summarize biological as well as clinical aspects of mantle cell lymphoma with a special focus on recent improvements in the therapy.

G. Lenz (✉) · M. Dreyling · W. Hiddemann
Department of Internal Medicine III, Großhadern Hospital,
Ludwig-Maximilians University,
81377 Munich, Germany
e-mail: georg.lenz@med3.med.uni-muenchen.de
Tel.: +49-89-70951
Fax: +49-89-70955550

Biology

Histology and immunophenotype

Mantle cell lymphoma is derived from a subset of naive pregerminal center cells, localized in primary follicles or in the mantle region of secondary follicles. Accordingly, the majority of cases display an unmutated immunoglobulin heavy chain locus [59]. Mantle zone, nodular or diffuse growth pattern may be observed [4, 60]. Cytologically, two subsets can be distinguished, the classic mantle cell lymphoma and the blastoid variant (approximately 10% of cases [9]).

The characteristic immunophenotype of mantle cells includes the co-expression of the pan-T-cell antigen CD5 and a variety of pan-B-cell antigens (CD19, CD20, CD22 and CD79a) and the HLA-DR antigen. In contrast to chronic lymphocytic leukemia (CLL), the cells are usually negative for CD23, although a weak expression may be detected by flow cytometry in some cases. They almost always bear surface IgM and often IgD, but are negative for the CD10 antigen.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Cytogenetics

Genetically, mantle cell lymphoma is characterized by the chromosomal translocation t(11; 14) (q13; q32), which results in a juxtaposition of the *bcl-1* gene locus to the Ig heavy chain promoter and the subsequent overexpression of the cell cycle regulator protein cyclin D1 in the vast majority of cases [47]. Cyclin D1 plays an important role in the cell cycle regulation by propelling cells from the G_1 into the S phase as the activated cyclin D1/cyclin-dependent kinase (CDK) inactivates the tumor suppressor retinoblastoma protein (pRb) [9]. However, cyclin D1 overexpression alone is not sufficient to induce lymphoma development [7]. Accordingly, in more than 80% of mantle cell lymphoma cases, secondary alterations can be detected, 40–50% with complex cytogenetic alterations [11, 50, 62].

Clinical features of presentation

The majority of mantle cell lymphoma cases are diagnosed at advanced Ann Arbor stages III or IV (Table 1). Extranodal involvement is found in approximately 90% of cases, including bone marrow, liver and gastrointestinal tract [8, 23, 45, 49, 58]. A characteristic extranodal presentation of mantle cell lymphoma is multiple lymphomatous polyposis of the intestine. However, this feature is frequently not diagnosed due to incomplete staging procedures [30]. Less common extranodal sites are skin, lung, breast or soft tissues. Central nervous system involvement is found in up to 4–22% of relapsed mantle cell lymphoma cases [43]. B-symptoms are described in less than 50% of cases (Table 1).

Prognostic factors

Important clinical prognostic factors that have been identified in previous studies are poor performance status, splenomegaly, anemia and age [3, 8, 13]. The published data on the prognostic value of morphologic parameters such as cytology or the growth pattern are contradictory [6, 8, 42, 55, 61]. Various studies confirmed the poor prognosis of *p53* mutations [21, 22, 63]. However, the most important biological prognostic factor in multiple series was the proliferation rate determined by the number of mitoses or the Ki67 staining index. In a study by Bosch et al., patients with >2.5 mitoses/high power field (HPF) had a median survival of only 24 months, whereas those with $\leq$2.5 mitoses/HPF had a survival of 50 months, clearly indicating the prognostic value of cell proliferation [8]. Similarly, in a large retrospective study of 350 patients with confirmed diagnosis of mantle cell lymphoma, different proliferation indices represented the most powerful prognostic marker, clearly superior to cytomorphology and clinical parameters [13]. These results have been confirmed by a recent RNA array study, which again identified cell proliferation markers as the most powerful prognostic tool in mantle cell lymphoma [47].

Clinical management

Radiation in early stages

The small number of patients with limited Ann Arbor stage I-II may potentially be cured by modified extended or involved field radiation. In addition, a recent study suggested an advantage of sequential radiochemotherapy [35]. In contrast, in advanced stage III-IV, the benefit of radiation therapy in addition to chemotherapy is not proven. Thus, local radiation therapy should only be performed in cases with bulky disease not responsive to conventional therapy.

Conventional chemotherapy

Mantle cell lymphoma has the poorest long-term survival of all lymphoma subtypes. Consequently, a wait-and-see strategy is not justified, although in advanced stages conventional chemotherapy represents only a non-curative treatment option. Different chemotherapeutic regimens achieve overall response rates of approximately 70%, with complete remissions in up to 20–40% of cases [40, 57, 64].

Table 1 Features of presentation

	N	Median age (yr)	Stage IV	Sex (m/f)	Bone marrow	Leukemic expression	Splenomegaly	GI tract
Berger et al. 1994 [5]	52	58% >60	89% (III + IV)	NA	82%	49%	59%	20%
Zucca et al.1995 [64]	65	64	72%	2/1	58%	20%	35%	15%
Norton et al.1995 [42]	66	62	82%	3.7/1	80%	NA	48%	12%
Fisher et al. 1995 [14]	36	55	NA	4/1	53%	NA	NA	19%
Pittaluga et al. 1995 [45]	55	68	62%	6.8/1	66%	NA	NA	NA
Hiddemann et al. 1996 [23]	573	63	75%	2.5/1	69%	NA	NA	NA
Velders et al. 1996 [58]	41	68	78%	1.6/1	80%	NA	NA	NA
Majlis et al. 1997 [37]	46	54	82% (III + IV)	1.7/1	69%	NA	NA	24%
Bosch et al. 1998 [8]	59	63	95% (III + IV)	3/1	81%	58%	44%	17%

yr years, *m* male, *f* female, *NA* not available

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

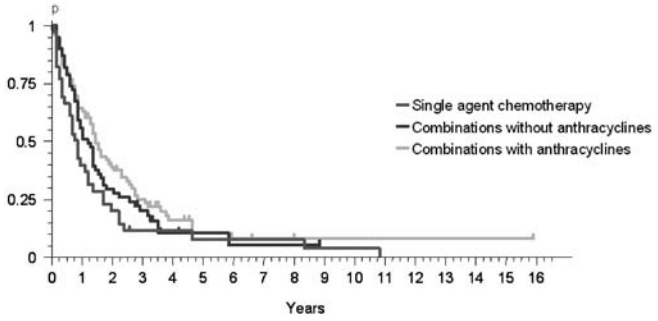

Fig. 1 Event-free interval after different chemotherapy regimens in MCL

The use of anthracycline-containing regimens was evaluated in various studies. In the only randomized study, no advantage of the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) in comparison to a non-anthracyclin combination (COP: cyclophosphamide, vincristine and prednisone) was detectable [39]. The overall response rate was 84% after COP and 89% after CHOP, with a median overall survival of 32 and 37 months, respectively. In contrast, in a retrospective study, Zucca and colleagues claimed a superiority of anthracycline-containing regimens with regard to the complete response rate, failure-free and overall survival in the low-risk group of mantle cell lymphoma patients [64]. Thus, although clinical studies did not clearly prove a superiority of anthracycline-containing combinations, CHOP-like regimens currently represent the standard therapeutic approach (Fig. 1).

Encouraging results have been achieved in various phase II studies implementing high-dose cytarabine (Ara-C). After a sequential CHOP-DHAP regimen (dexamethasone, high-dose cytarabine and cisplatin), over 80% of the treated patients obtained a complete remission [34]. Similarly, high response rates of more than 90% could be achieved by a dose-intensified approach of the M.D. Anderson Cancer Center applying an alternating regimen of Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) with high-dose cytarabine and methotrexate [46]. As these data suggest a high efficacy of high-dose cytarabine in mantle cell lymphoma, this concept is currently being tested by the European mantle cell lymphoma Network.

The use of purine analogs (fludarabine or cladribine; 2-CdA) in the therapy of mantle cell lymphoma has been investigated in different studies [12, 15, 48]. Single-agent fludarabine showed only moderate activity with response rates of 32–41%. In contrast, combinations with alkylating agents or anthracyclines were able to achieve higher remission rates [10, 27, 48].

Other chemotherapy regimes as gemcitabine, dexamethasone and cisplatin or cisplatin, fludarabine and cytarabine achieved remarkable response rates in up to 88% of relapsed or refractory mantle cell lymphoma [41, 51]. However, response duration was short.

Interferon-α

In various phase II studies, a prolonged progression-free survival after an interferon-α maintenance has been observed similarly to follicular lymphomas [24, 54]. However, the number of investigated patients was too low to reach statistical significance. Nevertheless, interferon-α may be part of future approaches, e.g., in combination with rituximab.

Monoclonal antibodies

In the past few years, various studies investigated the efficacy of the anti-CD20 antibody rituximab in mantle cell lymphoma. The monotherapy with rituximab showed only a moderate activity, with partial response rates of approximately 20–40% [16, 17, 56]. In contrast, the combined immunotherapy (rituximab and CHOP) achieved remarkably high overall and complete response rates (96 and 48%) [28], suggesting a chemosensitizing effect of rituximab. Nevertheless, the higher response rates did not translate into a prolonged progression-free survival (median progression-free survival: 16.6 months; Table 2).

More encouraging results were recently published by Hiddemann et al. [27]. In a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG), the combination of FCM chemotherapy (fludarabine, cyclophosphamide and mitoxantrone) and rituximab was compared to FCM alone in refractory and relapsed mantle cell lymphoma. The addition of rituximab resulted in significantly improved complete remission

Table 2 Rituximab and chemotherapy in mantle cell lymphoma

Authors	N	Regimen	CR/OR
Hiddemann et al. 2002 [27]	24	R-FCM Rituximab 375 mg/m^2/dx1 Fludarabine 25 mg/m^2/dx3 Cyclophosphamide 200 mg/m^2/dx3 Mitoxantrone 8 mg/m^2/d x 1	33%/62%[a]
Howard et al. 2002 [28]	40	R-CHOP	48%/96%
Hiddemann et al. 2002 [27]	40	R-CHOP	45%/90%[a]

n number of patients, *CR* complete remission, *OR* overall response
[a] Significant improvement in comparison to chemotherapy alone

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

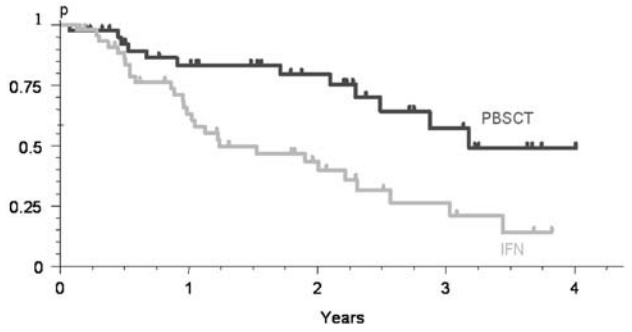

Fig. 2 Prospectively randomized comparison of progression-free survival after peripheral blood stem cell transplantation and interferon-α maintenance. Patients assigned to stem cell transplantation experience significantly longer progression-free survival

rates (33 vs. 0%; p=0.003) and a 20% increase of overall response rates (62 vs. 43%), clearly indicating the superiority of a combined immunochemotherapy in mantle cell lymphoma (Table 2). After a median follow-up of 19 months (23 months for patients alive) these high remission rates resulted in a significantly improved overall survival (p=0.005). In another prospective, randomized study of the GLSG, the addition of rituximab in the first line therapy (R-CHOP) resulted in a similar improvement of remission rates (overall response: 90 vs. 71%; p=0.031; complete remission: 45 vs. 10%; p<0.001; Table 2) [27]. However, longer follow-up is necessary to evaluate the impact on overall survival. Future study concepts focus on the role of rituximab maintenance and in vivo purging prior to autologous stem cell transplantation [18].

Another innovative approach is the application of radio (^{131}iodine or ^{90}yttrium) labeled anti-CD20 antibodies in a conventional or myeloablative dosage. Different studies achieved remarkably high and long-lasting remissions in relapsed or refractory mantle cell lymphoma patients [19].

Autologous stem cell transplantation

One of the options, established in the meantime, in the treatment of mantle cell lymphoma is myeloablative therapy followed by autologous stem cell transplantation. This approach significantly improves the progression-free survival and may partially overcome the therapeutically dilemma of mantle cell lymphoma.

In a randomized prospective study of more than 200 patients, the European mantle cell lymphoma Network evaluated a consolidating myeloablative radiochemotherapy followed by autologous stem cell transplantation after a CHOP-like induction [26]. Patients receiving such a myeloablative consolidation achieved a significantly longer disease-free survival and a borderline improvement of overall survival in comparison to interferon-α maintenance therapy (Fig. 2). In contrast, the efficacy in relapsed mantle cell lymphoma seems to be limited [52]. Consequently, high-dose-consolidation in first remission should be considered as standard therapy in younger mantle cell lymphoma patients. However, even after such a dose-intensified approach the majority of patients will finally relapse, possibly due to a contamination of the harvested stem cells with lymphoma cells. Standard immunological in vitro purging procedures failed to eradicate these circulating mantle cells [2, 53]. In contrast, rituximab in vivo purging prior to autologous stem cell transplantation may be more effective. Remarkably high overall survival rates of 89% after a median follow-up of 35 months have been reported after such an antibody-based concept [18]. However, these encouraging results have to be confirmed in prospective phase III studies.

Allogenic transplantation

In mantle cell lymphoma the only curative therapy so far is allogenic stem cell transplantation. Different studies showed that long-lasting complete remission can be achieved even in patients with relapsed or refractory mantle cell lymphoma [1, 33, 38]. Khouri et al. [31] reported that allogenic transplantation resulted in an overall and failure-free survival of 55% at 3 years. Molecular remission was achieved in five of seven patients within 7 months post transplant. These data strongly support the role of a graft-versus-lymphoma effect in mantle cell lymphoma. However, infectious complications are common and transplant-related toxicity and mortality may be high even after a dose-reduced conditioning regimen.

New therapeutic modalities

A new molecular targeting agent in the treatment of mantle cell lymphoma is the specific inhibitor of the cyclin-dependent kinase (CDK)4-cyclin D1 complex flavopiridol. Kouroukis et al. [32] investigated the efficacy of flavopiridol given three times per week every 3 weeks in a recent phase II study. However, neither this scheme (no complete remissions and only 11% partial responses) nor a 72-h continuous infusion [36] showed a significant efficacy in relapsed or refractory mantle cell lymphoma. As cell culture experiments suggest a chemosensitizing effect, flavopiridol might be more effective in combination with chemotherapy.

The proteasome inhibitor Bortezomib (Velcade, formerly PS-341) represents another molecular targeted approach in the treatment of mantle cell lymphoma. Bortezomib is highly effective in mantle cell lymphoma derived cell lines and SCID mouse models by sensitizing lymphoma cells to apoptosis [44]. In addition, Bortezomib showed its efficacy in a recent phase II study of the M.D. Anderson Cancer Center; five of eight (62.5%) previously heavily pre-treated mantle cell lymphoma patients responded to a Bortezomib therapy at a dose of 1.5 mg/m^2 [20].

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Conclusion

Mantle cell lymphoma remains one of the most challenging problems in the diagnosis and therapy of malignant lymphoma. So far, CHOP-like combinations have represented the standard therapeutic approach. Recent prospective randomized studies have confirmed the benefit of a combined immunochemotherapy with rituximab in newly diagnosed as well as relapsed mantle cell lymphoma. In addition, in younger patients myeloablative radiochemotherapy followed by autologous stem cell transplantation represents the standard approach. Unfortunately, the only curative approach is allogenic bone marrow transplantation, indicating that new therapeutic strategies are warranted to improve the clinical outcome of mantle cell lymphoma.

References

1. Adkins D, Brown R, Goodnough LT, Khoury H, Popovic W, DiPersio J (1998) Treatment of resistant mantle cell lymphoma with allogeneic bone marrow transplantation. Bone Marrow Transplant 21:97–99
2. Andersen NS, Donovan JW, Borus JS, Poor CM, Neuberg D, Aster JC, Nadler LM, Freedman AS, Gribben JG (1997) Failure of immunologic purging in mantle cell lymphoma assessed by polymerase chain reaction detection of minimal residual disease. Blood 90:4212–4221
3. Andersen NS, Jensen MK, de Nully Brown P, Geisler CH (2002) A Danish population-based analysis of 105 mantle cell lymphoma patients. Incidences, clinical features, response, survival and prognostic factors. Eur J Cancer 38:401–408
4. Banks PM, Chan J, Cleary ML, Delsol G, De Wolf-Peeters C, Gatter K, Grogan TM, Harris NL, Isaacson P, Jaffe ES (1992) Mantle cell lymphoma. A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol 16:637–640
5. Berger F, Felman P, Sonet A, Salles G, Bastion Y, Bryon PA, Coiffier B (1994) Nonfollicular small B-cell lymphomas: a heterogeneous group of patients with distinct clinical features and outcome. Blood 83:2829–2835
6. Bernard M, Gressin R, Lefrere F, Drenou B, Branger B, Caulet-Maugendre S, Tass P, Brousse N, Valensi F, Milpied N, Voilat L, Sadoun A, Ghandour C, Hunault M, Leloup R, Mannone L, Hermine O, Lamy T (2001) Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia 15:1785–1791
7. Bodrug SE, Warner BJ, Bath ML, Lindeman GJ, Harris AW, Adams JM (1994) Cyclin D1 transgene impedes lymphocyte maturation and collaborates in lymphomagenesis with the myc gene. Embo J 13:2124–2130
8. Bosch F, Lopez-Guillermo A, Campo E, Ribera JM, Conde E, Piris MA, Vallespi T, Woessner S, Montserrat E (1998) Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. Cancer 82:567–575
9. Campo E, Raffeld M, Jaffe ES (1999) Mantle-cell lymphoma. Semin Hematol 36:115–127
10. Cohen BJ, Moskowitz C, Straus D, Noy A, Hedrick E, Zelenetz A (2001) Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 42:1015–1022
11. Cuneo A, Bigoni R, Rigolin GM, Roberti MG, Bardi A, Piva N, Milani R, Bullrich F, Veronese ML, Croce C, Birg F, Dohner H, Hagemeijer A, Castoldi G (1999) Cytogenetic profile of lymphoma of follicle mantle lineage: correlation with clinicobiologic features. Blood 93:1372–1380
12. Decaudin D, Bosq J, Tertian G, Nedellec G, Bennaceur A, Venuat AM, Bayle C, Carde P, Bendahmane B, Hayat M, Munck JN (1998) Phase II trial of fludarabine monophosphate in patients with mantle-cell lymphomas. J Clin Oncol 16:579–583
13. Dreyling MH (2002) The increasing role of prognostic factors in the choice of treatment—Mantle Cell Lymphoma. Ann Oncol 13
14. Fisher RI, Dahlberg S, Nathwani BN, Banks PM, Miller TP, Grogan TM (1995) A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. Blood 85:1075–1082
15. Foran JM, Rohatiner AZ, Coiffier B, Barbui T, Johnson SA, Hiddemann W, Radford JA, Norton AJ, Tollerfield SM, Wilson MP, Lister TA (1999) Multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma, Waldenstrom's macroglobulinemia, and mantle-cell lymphoma. J Clin Oncol 17:546–553
16. Foran JM, Rohatiner AZ, Cunningham D, Popescu RA, Solal-Celigny P, Ghielmini M, Coiffier B, Johnson PW, Gisselbrecht C, Reyes F, Radford JA, Bessell EM, Souleau B, Benzohra A, Lister TA (2000) European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 18:317–324
17. Ghielmini M, Schmitz SF, Burki K, Pichert G, Betticher DC, Stupp R, Wernli M, Lohri A, Schmitter D, Bertoni F, Cerny T (2000) The effect of Rituximab on patients with follicular and mantle-cell lymphoma. Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 11:123–126
18. Gianni AM, Magni M, Martelli M, Di Nicola M, Carlo-Stella C, Pilotti S, Rambaldi A, Cortelazzo S, Patti C, Parvis G, Benedetti F, Capria S, Corradini P, Tarella C, Barbui T (2003) Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood 102:749–755
19. Gopal AK, Rajendran JG, Petersdorf SH, Maloney DG, Eary JF, Wood BL, Gooley TA, Bush SA, Durack LD, Martin PJ, Matthews DC, Appelbaum FR, Bernstein ID, Press OW (2002) High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. Blood 99:3158–3162
20. Goy A, East K, Mesina O, Cabanillas F, Fayad L, Hagemeister F, McLaughlin P, Pro B, Romaguera J, Younes A, Wang M, Ford R, Gilles F, Scheinkein P, Trehu E, Rodriguez A (2003) Report of a phase II study of proteasome inhibitor Bortezomib in patients with relapsed or refractory indolent and aggressive B-cell lymphomas. Hematol J 4[Suppl 2]: 129
21. Greiner TC, Moynihan MJ, Chan WC, Lytle DM, Pedersen A, Anderson JR, Weisenburger DD (1996) *p53* mutations in mantle cell lymphoma are associated with variant cytology and predict a poor prognosis. Blood 87:4302–4310
22. Hernandez L, Fest T, Cazorla M, Teruya-Feldstein J, Bosch F, Peinado MA, Piris MA, Montserrat E, Cardesa A, Jaffe ES, Campo E, Raffeld M (1996) *p53* gene mutations and protein overexpression are associated with aggressive variants of mantle cell lymphomas. Blood 87:3351–3359
23. Hiddemann W, Brittinger G, Tiemann M, Parwaresch R, Stein H, Lister TA, Norton AJ, Pittaluga S, De Wolf-Peeters C, Van Hoof A, Coiffier B, Berger F, Kluin-Nelemans JC, Van Krieken JH, Kluin PM, Cavalli F, Roggero E, Pedrinis E, Montserrat E, Piris MA, Unterhalt M (1996) Presentation features and clinical course of Mantle Cell Lymphomas—Results a European survey. Ann Oncol 7:22
24. Hiddemann W, Unterhalt M, Herrmann R, Woltjen HH, Kreuser ED, Trumper L, Reuss-Borst M, Terhardt-Kasten E, Busch M, Neubauer A, Kaiser U, Hanrath RD, Middeke H, Helm G, Freund M, Stein H, Tiemann M, Parwaresch R (1998) Mantle-cell lymphomas have more widespread disease and a

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.