ARTICLE

The addition of rituximab to fludarabine and cyclophosphamide chemotherapy results in a significant improvement in overall survival in patients with newly diagnosed mantle cell lymphoma: results of a randomized UK National Cancer Research Institute trial

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ABSTRACT

Mantle cell lymphoma is an incurable and generally aggressive lymphoma that is more common in elderly patients. Whilst a number of different chemotherapeutic regimens are active in this disease, there is no established gold standard therapy. Rituximab has been used widely to good effect in B-cell malignancies but there is no evidence that it improves outcomes when added to chemotherapy in this disease. We performed a randomized, open-label, multicenter study looking at the addition of rituximab to the standard chemotherapy regimen of fludarabine and cyclophosphamide in patients with newly diagnosed mantle cell lymphoma. A total of 370 patients were randomized. With a median follow up of six years, rituximab improved the median progression-free survival from 14.9 to 29.8 months (P<0.001) and overall survival from 37.0 to 44.5 months (P=0.005). This equates to absolute differences of 9.0% and 22.1% for overall and progression-free survival, respectively, at two years. Overall response rates were similar, but complete response rates were significantly higher in the rituximab arm: 52.7% *vs*. 39.9% (P=0.014). There was no clinically significant additional toxicity observed with the addition of rituximab. Overall, approximately 18% of patients died of non-lymphomatous causes, most commonly infections. The addition of rituximab to fludarabine and cyclophosphamide chemotherapy significantly improves outcomes in patients with mantle cell lymphoma. However, these regimens have significant late toxicity and should be used with caution. This trial has been registered (ISRCTN81133184 and *clinicaltrials.gov identifier*:00641095) and is supported by the UK National Cancer Research Network.

Introduction

Mantle cell lymphoma (MCL) is an uncommon and usually aggressive form of non-Hodgkin lymphoma with an annual incidence of approximately 1 per 100,000 of the population. In younger patients, the treatment of choice includes a high-dose cytarabine-containing regimen usually followed by autologous stem cell transplantation.[1,2] However, with a median age at presentation in the mid sixth decade, such therapy is not applicable to the majority of patients. There is no generally accepted

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standard of care for older patients and a variety of treatments have been widely used. Newer therapeutic approaches are clearly needed as, despite improvements in outcome for patients treated within trial cohorts,[3] recent SEER data show there has been no improvement in outcome for this disease over the last 20 years.[3]

Mantle cell lymphoma expresses the pan-B-cell surface antigen CD20, and with the advent of specific monoclonal antibodies targeting this antigen, a new therapeutic option became available. Rituximab (Rituxan, Mabthera) is a chimeric anti-CD20 monoclonal antibody that is widely used in lymphoproliferative disorders. It has wide international regulatory approval for use in both diffuse large B-cell and follicular lymphoma. As a single agent, rituximab produces response rates of approximately 35% in MCL[5,6] and when added to the standard chemotherapeutic regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) within a phase II single arm study the combination demonstrated a very high overall response rate.[7] There have subsequently been three randomized trials involving the addition of rituximab to a standard chemotherapeutic regimen in which patients with MCL have been included. All of these trials included a variety of 'low-grade' lymphomas, including MCL. Two of these studies considered the addition of rituximab as part of the initial therapy to CHOP[8] and MCP[9] (mitoxantrone, chlorambucil and prednisolone). In both trials, no difference in progression-free survival (PFS) or overall survival (OS) was demonstrable within the subset of patients with MCL; however, only 122 and 90 patients were randomized in these trials, respectively. A subsequent relapse study examined the addition of rituximab to FCM (fludarabine, cyclophosphamide and mitoxantrone).[10] This study did demonstrate an improvement in OS in the rituximab containing arm; however, there were only 24 patients with MCL in each arm. A subsequent meta-analysis of all three studies suggested an OS benefit for the addition of rituximab.[11] However, no individual phase III study has yet demonstrated such a benefit, and thus the true impact of rituximab is still unclear.

The purine nucleoside analog class of drugs have demonstrable activity in the treatment of MCL.[12-15] Fludarabine is the most widely used nucleoside analog and when combined with cyclophosphamide in patients with MCL high response rates are achieved.[12] This combination has the attraction of not including an anthracycline, which can be associated with cardiac toxicity in elderly patient populations and can be delivered as an oral combination. Given this, in 2002, a UK-based randomized trial was initiated exploring the addition of rituximab to oral FC.

Table 1. Base-line characteristics.

	F/C n=184 n (%)	F/C/R n=186 n (%)
Age at randomization		
Median (range)	66 (37 - 85)	66 (36 - 88)
Gender		
Male	146 (79.3)	137 (73.7)
Female	38 (20.7)	49 (26.3)
ECOG[1]		
0	87 (47.3)	93 (50.0)
Performance status		
1	64 (34.8)	62 (33.3)
2	15 (8.2)	17 (9.1)
3	5 (2.7)	0 (0.0)
4	1 (0.5)	0 (0.0)
Missing	12 (6.5)	14 (7.5)
B symptoms		
Absent	106 (57.6)	97 (52.2)
Present	74 (40.2)	81 (43.5)
Missing	4 (2.2)	8 (4.3)
Stage		
I	2 (1.1)	4 (2.2)
II	11 (6.0)	15 (8.1)
III	32 (17.4)	25 (13.4)
IV	134 (72.8)	134 (72.0)
Missing	5 (2.7)	8 (4.3)
Serum LDH level		
Normal	99 (53.8)	96 (51.6)
Elevated	80 (43.5)	77 (41.4)
Missing	5 (2.7)	13 (7.0)
MIPI risk group		
Low	45 (24.5)	37 (19.9)
Intermediate	63 (34.2)	75 (40.3)
High	60 (32.6)	55 (29.6)
Missing	16 (8.7)	19 (10.2)

[1]Eastern Cooperative Oncology Group; [2]lactate dehydrogenase; [3]the Mantle Cell Lymphoma International Prognostic Index.

Methods

Study design

The trial began as a randomized 2-stage phase II study with eligible patients given either the standard chemotherapeutic regimen of FC or same regimen with the addition of rituximab (FCR). A Simon's design was used, with a target response rate of more than 60%, compared to less than 40%, with 90% power and 10% two-sided significance level (target sample size: 82 patients).

After meeting the target response (reviewed by an independent data monitoring committee), the trial was extended into phase III, powered to detect an improvement in the 3-year OS rate of 11% (55% FC *vs.* 66% FCR) with 80% power and 5% two-sided test of statistical significance (log rank test), requiring 370 patients in total.

Secondary end points included progression-free survival (PFS), response and toxicity.

Ethics and study management

The study complied with the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice guidelines. The protocol was approved by an independent ethics committee and by local review boards at each participating institution.

Patient selection

Patients aged over 18 years with previously untreated MCL were eligible. Central pathological confirmation of MCL diagnosis including cyclin D1 overexpression or evidence of t(11:14) was performed retrospectively, but was not required for inclusion in the study. Patients required adequate organ function and a life expectancy of at least three months.

Study treatment

Patients received oral 40 mg/m^2 fludarabine and 250 mg/m^2 cyclophosphamide on days 1-3 of a 28-day cycle. Patients randomized to FCR received intravenous (iv) 375 mg/m^2 rituximab on day 1 of each cycle. In patients intolerant of oral FC, treatment could be given intravenously: cyclophosphamide at the same dose

Table 2. Subgroup analysis.

Subgroup	OS			PFS	
	HR(95% CI)	P*	Events/n	HR(95% CI)	P*
B symptoms		P=0.06			P=0.05
Absent	0.54 (0.37, 0.79)		116/203	0.42 (0.30, 0.59)	
Present	0.91 (0.63, 1.32)		116/155	0.71 (0.50, 1.00)	
Stage		0.99			0.70
I/II	0.64 (0.21, 1.97)		14/32	0.42 (0.16, 1.08)	
III	0.74 (0.38, 1.45)		37/57	0.57 (0.31, 1.05)	
IV	0.74 (0.55, 0.99)		180/268	0.54 (0.41, 0.71)	
Serum LDH		0.15			0.65
Normal	0.59 (0.40, 0.86)		109/195	0.44 (0.31, 0.61)	
Elevated	0.87 (0.60, 1.25)		119/157	0.70 (0.49, 0.99)	
Age		0.72			0.94
<70	0.65 (0.46, 0.92)		133/233	0.51 (0.37, 0.69)	
≥70	0.72 (0.49, 1.05)		107/137	0.53 (0.37, 0.77)	
MIPI risk group		0.70			0.55
Low	0.50 (0.25, 0.99)		37/82	0.36 (0.21, 0.64)	
Intermediate	0.73 (0.47, 1.13)		82/138	0.57 (0.38, 0.84)	
High	0.72 (0.48, 1.08)		97/115	0.55 (0.37, 0.82)	

P-value for the interaction.

and 25 mg/m^2 fludarabine.[16]

Supportive care was provided according to institutional practice but *Pneumocystis jirovecci* (PJP) prophylaxis was mandatory, as was the use of irradiated blood products.

Patients received 4 cycles of therapy before re-staging. If they showed no response or had already progressed they were taken off study. Those patients with responsive disease were treated to maximal response or a maximum of 8 cycles of treatment. At the completion of therapy, patients were re-staged and followed up as according to institutional practice. Follow up scans did not follow a standardized schedule. Standard response criteria were adopted.[17] PET scans were not performed. Adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (v.3.0). Following treatment, patients were not permitted to receive any form of maintenance or consolidation therapy.

Statistical analysis

All time-to-event analyses were performed on an intention to treat basis; however, response and toxicity analyses were limited to patients who received at least one dose of treatment. OS was measured from the date of randomization until the date of death and PFS from the date of randomization until the date of progression or death. Patients who did not experience an event were censored at the date last seen. OS and PFS distributions were examined using Kaplan-Meier curves, and Cox proportional hazards models after confirming the assumption of proportional hazards. All analyses were performed using Stata software (v.12.1) (StataCorp, TX, USA).

Results

Patients' characteristics

A total of 370 patients were randomized (n=156 phase II and n=214 phase III) between the 2nd of September 2002 and the 2nd of December 2010 from 96 centers in the UK, Poland and Australia. Patients' characteristics were well balanced between arms (Table 1). Median age at randomization was 66 years with a male predominance of 3:1. The vast majority of the patients had intermediate- or high-risk disease, as assessed by the Mantle Cell International Prognostic Index (MIPI).[18]

Diagnostic material of 297 patients was centrally reviewed. Of these patients, 19 did not have sufficient material to confirm a diagnosis. From the remaining 278 patients there were 11 patients (4%) with incorrect diagnoses: 4 marginal zone lymphomas, one diffuse large B-cell lymphoma, one chronic lymphocytic leukemia, 4 with no evidence of lymphoma (on the material centrally reviewed) and one patient diagnosed with MCL which did not express cyclin D1.

Compliance

The addition of rituximab did not affect the tolerance of FC chemotherapy, with the number of patients receiving 4 cycles or more being higher in the FCR arm than the FC arm: 128 (70.3%) *vs.* 102 (55.7%) (*P*=0.004). The proportion of patients whose chemotherapy was delayed or dose-reduced was similar in the two arms; 16.3% (142 of 877) of FC cycles and 15.3% (149 of 971) of FCR cycles were delayed and less than 90% of one or more drugs was given in 18.5% (162 of 877) of cycles of FC and 23.5% (236 of 971) of FCR [20.9% (203 of 971) of FCR cycles if only FC dose reductions were considered].

Efficacy

More patients in the FCR arm achieved an objective disease response (CR/CRu/PR) at the end of treatment than in the FC arm: 137 (73.7%) *vs.* 125 (68.3%). However, this was not statistically significant (*P*=0.26). The proportion of complete responses (CR and CRu) was significantly higher in the FCR arm: 98 (52.7%) *vs.* 73 (39.9%), (*P*=0.014).

Fewer patients experienced progression of disease on therapy in the FCR arm [16 (8.6%) *vs.* 27 (14.8%)] although this did not reach statistical significance (*P*=0.066).

Figure 1 shows Kaplan Meier curves for OS and PFS. The median OS was 44.5 months in the FCR arm and 37.0 months in the FC arm. The patients who received FCR had a 31% reduction in the risk of death: hazard ratio (HR) 0.69, 95%CI: 0.54-0.90. At two years, the survival proportions are

59.8% (95%CI: 52.3-66.5) in the FC arm and 68.8% (95%CI: 61.6-74.9) in the FCR arm.

The improvement in PFS was even greater (median PFS: 29.8 months with FCR *vs.* 14.9 with FC) with a reduction in the risk of death or progression of 47% for patients given FCR (HR 0.53, 95%CI: 0.42-0.67; *P*<0.001). This represents an absolute difference of 22.1% in PFS at two years. The proportional hazards assumption held for PFS (*P*=0.11).

More FCR patients received 4 cycles or more [128 (70.3%) *vs.* 102 (55.7%)], so it is plausible that adding rituximab allowed more cycles to be delivered, which might account for the observed treatment benefit. However, there was no clear pattern between HR and number of cycles. The interaction *P*-value was driven by the large HR among patients receiving 2 cycles (5.86) and when these are excluded the interaction *P*-value becomes statistically non-significant (*P*=0.17). Therefore, the overall HR of 0.69 for FCR *versus* FC is unlikely to be due to the number of cycles.

Overall survival and PFS results held when patients without a centrally confirmed MCL diagnosis were excluded. The PFS results also held when patients who were given further systemic treatment (n=20) before progression were censored.

Table 2 shows the HRs for OS and PFS according to prespecified base-line factors. There was no strong evidence of a difference in treatment effect within any of the subgroups.

Toxicity

The treatment-related mortality (TRM) was low and similar between the 2 arms. Five (2.7%) patients in the FC arm and 6 (3.2%) in the FCR arm were recorded as dying from treatment-related causes, predominantly sepsis.

The incidence of grade III/IV toxicity was similar between the two treatment arms (*P*=0.12) (Table 3A), and although more patients experienced grade III/IV hematologic toxicities in the FCR arm [105 (57.4%) *vs.* 125 (67.2%)] this did not reach statistical significance (*P*=0.051). There was more grade III/IV thrombocytopenia [53 (28.5%) *vs.* 33 (18.0 %); *P*=0.017] in the FCR arm. However, this did not result in any clinically significant bleeding episodes. There was more leukopenia [(32 (17.2%) *vs.* 18 (9.8%); *P*=0.039)] in the FCR arm, although there was no increase in neutropenia or observed infections. There were more allergic reactions in the rituximab-containing regimen, in keeping with the known infusion-related toxicity of this agent, although grade III/IV events occurred in only 12 (6.5%) patients.

Although toxicity rates were slightly higher in the FCR arm, this may, in part, be due to the fact that these patients received more cycles of therapy than in the FC arm. For those toxicities recorded in the first 4 cycles (Table 3B), there is no significant difference between the arms with 85 (46.5%) patients in the FC arm experiencing a grade 3/4 hematologic toxicity *versus* 95 (51.1%) in the FCR arm (*P*=0.37). The rates of non-hematologic toxicity were almost identical: 69 (37.7%) patients in the FC arm experiencing a toxicity *versus* 69 (37.1%) in the FCR arm (*P*=0.90).

Late toxicity

At a median follow up of almost 6.02 years, a total of 240 patients have died, 132 (71.7%) in the FC arm and 108 (58.1%) in the FCR arm. The most common cause of death was lymphoma, accounting for 94 (71.2%) and 66 (61.1%) deaths in each arm. Thirty patients in the FC arm and 36 patients in the FCR arm died of other causes. Approximately one-third were secondary to infections (12 FC, 15 FCR) of which only one was classed as an opportunistic infection (*Mycobacterium tuberculosis*). The majority of other deaths were either second malignancies (7 in each arm, comprising 2 cases of AML and 5 various solid tumors in both arms) or cardiac events (5 post FC and 7 post FCR).

Discussion

With a median follow up of 6.02 years, this study has demonstrated that the addition of rituximab to FC chemotherapy leads to a significant improvement in both PFS and OS for patients with MCL. The addition of rituximab produces a modest increase in hematologic toxicity, but, importantly, no increase in neutropenia or infections, with no clinically significant difference in long-term toxicity.

The median age of the study population was 66 years making this a trial of predominantly elderly patients. The toxicity associated with this regimen is observed in the dose adjustments required throughout. Just below 40% of patients in both arms received less than the planned dose of one or more drug during at least one cycle. Despite this, the TRM was low in both arms (approx. 3%) but this might account for the relatively high number of patients experiencing disease progression on therapy. The other finding of concern is the number of patients who died following therapy of causes other than lymphoma, principle amongst these being infection. The propensity for patients to be at risk from opportunistic infections following purine analog therapy is well known because of the lymphoid suppression that can result

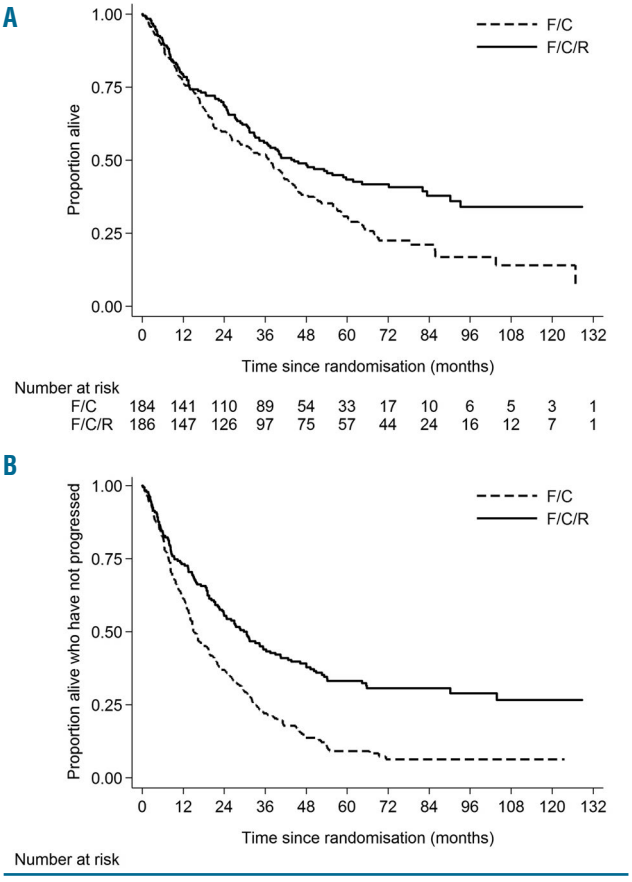

Figure 1. Kaplan Meier curves. (A) Overall Survival: HR (95% CI) 0.72 (0.55-0.94); *P*=0.016. (B) Progression Free Survival: HR (95% CI) 0.54 (0.42-0.69); *P*<0.001.

from it.[19] However, only one patient had a true opportunistic infection (TB) in this series.

A recent randomized trial comparing FCR with R-CHOP in elderly patients with MCL showed a survival benefit in favor of R-CHOP.[20] The findings in the FCR arm of that study are virtually identical to those obtained in the current study. They described greater hematologic toxicity in the FCR arm and more progressive disease on therapy: 14% to our 8.6%. But as we found, a significant number of patients died whilst in remission of their lymphoma, usually of infection.

The addition of rituximab to FC has also been explored in a large randomized trial in chronic lymphocytic leukemia (CLL).[21] This demonstrated a statistically significant increase in both PFS and OS in favor of the rituximab treatment arm. Toxicity problems were similar, with dose reductions secondary to neutropenia observed in over one-third of cycles and significant late effects, with approximately 50% of patients dying from causes other than leukemia.

The delayed toxicity following FC-based therapy impacts on the subsequent delivery of treatment at the time of relapse. Another CLL trial[22] considered the outcome of patients who received 3 different chemotherapy regimens, one of which was FC. Following progression, this group of patients had the worst outcome. It seems plausible that this inability to re-treat patients after relapse following FC-based therapy explains the survival difference observed in the Kluin-Nelemans[20] study in favor of R-CHOP. In that trial, the R-CHOP treated patients had a superior outcome despite a very similar time to treatment failure. Interestingly, in those patients progressing on FCR, the median survival was only five months post induction.

Does a survival benefit in favor of rituximab with FC mean

Table 3A. Toxicity.

Toxicity III/IV	In cycles 1-4		At any point	
	FC n=183	FCR n=186	FC n=183	FCR n=186
Hematologic				
Anemia	20 (10.9)	19 (10.2)	25 (13.7)	25 (13.4)
Neutropenia	74 (40.4)	84 (45.2)	88 (48.1)	105 (56.5)
Thrombocytopenia	23 (12.6)	26 (14.0)	33 (18.0)	53 (28.5)
Leukopenia	11 (6.0)	19 (10.2)	18 (9.8)	32 (17.2)
Any hematologic	85 (46.5)	95 (51.1)	105 (57.4)	125 (67.2)
Non-hematologic				
Fatigue	14 (7.7)	11 (5.9)	16 (8.7)	13 (7.0)
Allergy	1 (0.5)	12 (6.5)	1 (0.5)	12 (6.5)
Infection	21 (11.5)	22 (11.8)	26 (14.2)	30 (16.1)
Fever	6 (3.3)	5 (2.7)	7 (3.8)	7 (3.8)
Constipation	1 (0.5)	0	1 (0.5)	0
Nausea	9 (4.9)	4 (2.2)	10 (5.5)	4 (2.2)
Vomiting	11 (6.0)	6 (3.2)	12 (6.6)	7 (3.8)
Anorexia	5 (2.7)	5 (2.7)	5 (2.7)	5 (2.7)
Diarrhea	6 (3.3)	3 (1.6)	7 (3.8)	4 (2.2)
Stomatitis	1 (0.5)	0	1 (0.5)	0
Hypotension	3 (1.6)	7 (3.8)	3 (1.6)	7 (3.8)
Bronchospasm	0	2 (1.1)	0	2 (1.1)
Cardiac	5 (2.7)	4 (2.2)	6 (3.3)	5 (2.7)
Pulmonary	10 (5.5)	10 (5.4)	12 (6.6)	12 (6.5)
Skin rash	9 (4.9)	6 (3.2)	10 (5.5)	7 (3.8)
Flushing	1 (0.5)	0	1 (0.5)	0
Headaches	3 (1.6)	1 (0.5)	4 (2.2)	2 (1.1)
Joint pain	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)
Neurological	2 (1.1)	1 (0.5)	2 (1.1)	3 (1.6)
Renal	0	1 (0.5)	0	1 (0.5)
Febrile neutropenia	8 (4.4)	6 (3.2)	10 (5.5)	10 (5.4)
Neutropenic sepsis	2 (1.1)	5 (2.7)	5 (2.7)	6 (3.2)
Gastrointestinal	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)
Other	17 (9.3)	13 (7.0)	18 (9.8)	18 (9.7)
Pancytopenia	1 (0.5)	3 (1.6)	5 (2 .7)	7 (3.8)
Any non-hematologic	69 (37.7)	69(37.1)	81 (44.3)	89 (47.9)
Any toxicity	111 (60.7)	118 (63.4)	132 (72.1)	147 (79.0)

Table 3B. Toxicity by cycle.

	In cycles 1-4		*P*	At any point		*P*
	FC	FCR		FC	FCR	
Any hematologic toxicity	85 (46.5)	95 (51.1)	0.37	105 (57.4)	125 (67.2)	0.051
Any non-hematologic toxicity	69 (37.7)	69 (37.1)	0.90	81 (44.3)	89 (47.9)	0.49
Any toxicity	111 (60.7)	118 (63.4)	0.58	132 (72.1)	147 (79.0)	0.12

that the same benefit would be seen if added to other standard chemotherapy approaches? The evidence in follicular lymphoma, where the benefit is consistent across a range of chemotherapies, would suggest this may be the case.[23-26] However, there have been two previous randomized trials[8,9] of rituximab in combination with CHOP and MCP in MCL where no survival benefit was observed. This is almost certainly a reflection of the small size of these studies, which were not sufficiently powered to demonstrate a difference. As rituximab had been shown to improve survival in randomized studies involving more common forms of lymphoma, the drug has been used widely in the context of MCL. However, in health care systems where specific evidence of a benefit is required, usually in the form of randomized evidence before a drug can be made generally available, it is increasingly important to design and complete appropriately powered studies. This study was predominantly performed in the UK and demonstrates that it is possible to carry out randomized studies in rare diseases.

In summary, the addition of rituximab to FC chemotherapy improves survival in patients with mantle cell lymphoma. However, the evidence would suggest that purine analog combinations should be used with caution in elderly patients.

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