Proposal to Remove Mustine from the List of Essential Cytotoxic Drugs

Summary of the request

Chlormethine hydrochloride [also known as Mechlorethamine, chlormethine, nitrogen mustard, mustine (UK) Mustargen (brand name in US and Canada)] is an alkylating agent, that has been in use for over half a century for the treatment of various cancers, most particularly lymphomas. For this indication, it has generally been used in combination with other drugs. Substituting mustine in these combinations with other less toxic drugs has proved to be equally clinically effective and the majority of oncologists do not use mustine containing regimens for Hodgkin's disease, while the use of mustine-containing regimens is no longer recommended for other types of lymphoma. Hence the request to remove this drug from the list of essential drugs for cancer therapy

Information supporting the request

Mustine has been used for several years as part of combination therapy for Hodgkins disease. The original mustine-containing combination used for this indication was known as MOPP (mechlorethamine, vincristine, procarbazine and prednisone), originally developed by the National Cancer Institute, Maryland, USA. This represented a significant advance in the treatment of this disease, whether used alone, or, much more frequently, in combination with radiation therapy (1). Following this, a large number of alternative chemotherapy regimens have been developed for this disease in an attempt to improve upon the therapeutic value of the MOPP combination, as well as to reduce side effects – both acute, and late effects, such assecondary malignancies and infertility. The results of some of these studies are summarized in table 1. In many of these regimens, chlormethine has been replaced by another alkylating agent. In others, alternating cycles of MOPP and other combinations have been used. There is no doubt that Hodgkin disease can be effectively treated without using chlormethine, and there is no evidence that substituting other alkylating agents, such as cyclophosphamide (COPP) or chlorambucil (LOPP) for mustine has any deleterious effect on therapeutic outcome. In addition, several combination regimens such as ABVD or BEACOPP have been shown to be at least as effective and most probably more effective than mustine–containing regimens (2). In the case of ABVD, in which follow up is sufficiently long, there are fewer late effects.

Mustine is generally used as a single agent and applied topically in the treatment of mycosis fungoides. However, currently many other modalities of treatment are available for this condition.

Chlormethine is a vesicant, and can give rise to severe tissue damage and ulceration if it leaks at the site of intravenous administration.

The primary reason to consider removal of mustine from the list of essential cytotoxic drugs is that it is at least as effective, if not more effective alternatives are available for the treatment of all diseases it has been used for in the past. In the case of Hodgkin disease, there is good evidence that several of the drug combinations more

frequently used today, which do not contain chlormethine, are superior to the original MOPP combination and in some cases, less toxic. In the case of other lymphomas, mustine-containing regimens are rarely used today, and again, more active drug combinations that do not contain mustine have been in use for many years. In cutaneous lymphoma (mycosis fungoides) many other therapies are available in addition to topical mustine. Mustine is not a component of standard therapy for any other tumor. Several alternatives to mustine are included in the essential drug list, e.g., cyclophosphamide, which is much more widely used in general, than chlormethine, and has the added advantage that it is not a vesicant. It is also an inexpensive drug.

11 of 12 oncologists surveyed by INCTR recommended removal of chlormethine from the list of essential cytotoxic drugs.

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Trials comparing efficacy of mustine

Reference	Setting	Subjects	Interventions	Findings
1 1994	Europe	192 stage IIIB and IV Hodgkin's disease	After 2 courses of MOPP, patients were randomized into 2 groups Group 1-6 further courses of MOPP Group 2 - 2 courses of ABVD followed by 2 courses of MOPP and 2 courses of ABVD	MOPP/ABVD significantly improved failure free survival rates, but had no improved influence on relapse free survival and survival rates
2 1991	Mexico	83 Advanced Hodgkin's disease	Randomised Group 1 MOPP Group 2 LOPP	No statistical difference between the two treatment groups in survival or relapse free-survival. LOPP combination was better tolerated with significantly less side effects
3 1982	France	94 Hodgkin's disease, clinical stages IIsub 3sub +A, IB, IIB, III A, IIIB	patients were treated at random by 3 MOPP or 3 CVPP (this was followed by splenectomy/radiation in both groups based on stage and response related criteria)	No significant difference between MOPP and CVPP
4 Probably 1980s	Probably US	327 Stage 3 and 4 Hodgkins Disease	Random selection Group 1 - MOPP Group 2 - M, VLB, PP Group3 - CCNU, O PP Group 4 - CCNU, VLB, PP	Complete remissions, duration of maintained remissions more with CCNU. When both CCNU and VLB are combined with PP there is a significant decrease of 68% ($p < .05$) in the failure rate over patients treated with MOPP
5 2005	Milan	811 Intermediate and advanced Hodgkin's disease	four randomised studies comparing MOPP and ABVD with or without radiation	Overall, ABVD contributed to significantly reduce the relative risk of lymphoma progression and death compared with the MOPP regimen.
6 1991	Britain	299 Stage III or IV Hodgkin's	Randomised Group 1 MOPP	There was no statistically significant difference between two groups in complete remission rates

Reference	Setting	Subjects	Interventions	Findings
		disease	Group2 LOPP	(63% for MOPP, 57% for LOPP), percentage of patients remaining disease free at 5 years (38% for MOPP, 35% for LOPP) and overall survival at 5 years (65% for MOPP, 64% for LOPP). LOPP had less side effects
7 2003	Intergroup trial	856 Adult patients with advanced Hodgkin's disease	randomly assigned Group 1 - ABVD Group 2 - MOPP/ABV	The rates of complete remission (76% v 80%, P =.16), failure-free survival at 5 years (63% v 66%, P =.42), and overall survival at 5 years (82% v 81%, P =.82) were similar for ABVD and MOPP/ABV. Clinically significant acute pulmonary and hematologic toxicity were more common with MOPP/ABV (P =.060 and.001, respectively). MDS, and leukaemia also more common with MOPP
8 1998	Children's Cancer group	111 children and adolescents with pathologically verified stages III and IV Hodgkin's disease.	Randomised trial Group A – MOPP/ ABVD Group 2 - ABVD + plus low-dose regional (extended-field) radiation therapy (EF RT)	Equivalent results for 4 yr event free survival (ABVD EFRT 87%; MOPP/ABVD 77% (P = .09) and overall survival (ABVD EF RT 90%; MOPP/ABVD 84% P = .45) were obtained by the addition of either MOPP or low-dose EF RT to the ABVD regimen
9 1996		63 Histologically proved glioma progressive despite prior radiotherapy.	Only one group MOP	Eight of 61 evaluable patients responded (13%), including 1 complete response. Several adverse reactions including myelosuppression
10 1984	USA	73 under 18 years with recurrent central nervous system tumor	randomized Group1 - MOPP Group 2 - OPP Patients were stratified according	No significant differences between the two groups in the duration of response or survival

Reference	Setting	Subjects	Interventions	Findings
			to the tumor type: (1) medulloblastoma (2) astrocytoma and other glioma (3) ependymoma (4) miscellaneous tumors	
11 1991	UK	115 supra-diaphragmatic, pathologically staged (PS) IA-IIB Hodgkins disease	randomised study Group 1 Mantle radiotherapy followed by adjuvant treatment with mustine, vinblastine, prednisolone, and procarbazine (MVPP) Group 2 mantle radiotherapy alone.	The overall 10-year survival after correction for intercurrent death was 92% with no difference between the two treatment groups(90% for RT alone and 95% for RT + MVPP P)
12 1976	Cairo	74 Non Hodgkin's lymphoma	Group 1 MOPP Group 2 CPP.	Complete remission for MOPP 60%, and for CPP 56%

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Table 2 Other trials where Mustine has been used, but not part of direct comparison

Hodgkins Lymphoma

REFERENCE	INTERVENTION	FINDINGS
Andrieu JM 1985	3 or 6 cycles of MOPP followed by Mantle field with or without mediastinal irradiation and/or inverted Y or lumboaortic field according to initial stage, presentation	Mediastinal irradiation can be avoided in patients with supradiaphragmatic disease without mediastinal involvement.
Andrieu JM 1981	3 cycles of MOPP, followed by selective supradiaphragmatic radiotherapy (RT) (mantle, or mantle without mediastinum, depending on initial findings), or inverted Y RT	sequence of chemotherapy MOPP - prophylactic splenectomy (according to initial stage) - selective nodal irradiation is an adequate treament for Hodgkin's disease
Bonadonna G 1979	six cycles of either MOPP or ABVD. Four to 6 weeks from the end of chemotherapy, complete plus partial responders were irradiated.	Chemotherapy-radiotherapy is confirmed to be a useful approach for advanced Hodgkin's disease, particularly in the presence of extranodal involvement, systemic symptoms, and nodular sclerosis
Bonfante V 1992	116 patients with favourable presentation treated with subtotal or total nodal radiotherapy alone. 85 cases with unfavourable presentation treated with 3MOPP - radiotherapy-3MOPP.	Confirms the usefulness of radiotherapy alone in favourable pathological stage IA.
Burgers 1991	Group 1Induction chemotherapy with eight cycles of MOPP Group 2combination of MOPP and ABVD	Equal complete remission rate
Rahim, M 1982	patients with recurrence after first remission induced by radiation therapy and/or MOPP were randomised Group 1- doxorubicin, oncovin, procarbazine and prednisolone (DOPP) Group 2 - further cycles of MOPP	DOPP combination is satisfactory and most likely superior to MOPP for producing complete remission in patients treated with radiotherapy and/or MOPP
Goldman JM 1981	Group 1- MOPP Group 2 - MOP (the same combination without prednisone) Patients with Stage IV disease were treated wither with MOPP	The incidence of complete remission was significantly higher for patients treated with MOPP than for those who received MOP. Duration of survival was also better in the former group

REFERENCE	INTERVENTION	FINDINGS
	or with MOPP plus bleomycin at low dosage (B-MOPP);	No significant difference in stage 1V disease also
Smith PG 1979	Recurrent Hodgkin's disease after disease free state after six courses of chemotherapy with MVPP were randomised for maintenance therapy Group 1 - intermittent treatment with vinblastine and procarbazine Group 2 - intermittent treatment with MVPP.	After a median follow-up period of nearly five years there was no significant difference between the two groups in either the rate of relapse or death rate.
Weiner 1991	median age of 12 years (range, 3 to 22 years) 4 cycles of MOPP alternating with 4 cycles of ABVD followed by low-dose radiotherapy (RT).	54 of 62 patients (87%) were in complete remission
NON HODGKINS		
Chisesi T 1991	ProMace/MOPP - six courses of chemotherapy, plus radiotherapy on bulky disease 2nd part of the study - randomized study Group 1 - ProMACE-MOPP Group 2 - MACOP-B..	. 53 pts (67%) achieved complete remission No differences in complete remission and disease free survival between the two groups
Other cancers		
Tattersall MHN 1982	cytologically confirmed malignant pleural effusions who had not received previous intra-cavitary chemotherapy were randomized to receive intracavitary Group 1 intracavitary adriamycin Group 2 nitrogen mustard Group 3 rolitetracycline	73% of patients responded to adriamycin, 70% to tetracycline and 44% to mustine.

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Table 3 Trials using drugs other than Mustine

Schellong 1999 Hodgkins disease in children	All groups underwent two cycles of vincristine, prednisone, procarbazine, and doxorubicin OPPA (girls) or OEPA (boys) for induction chemotherapy. TG2 and TG3 continued on additional two or four cycles, respectively, of cyclophosphamide, vincristine, prednisone, and procarbazine COPP. Low-dose radiotherapy was given to the initially involved sites, ie, reduced involved field	OEPA is a satisfactory alternative to OPPA. Radiotherapy can be confined to involved sites when combined with appropriate chemotherapy. The DAL-HD-90 regimen represents a comprehensive treatment program for all stages of pediatric HD and offers a favorable benefit/risk ratio, combining excellent disease control, moderate acute toxicity, and reduced long-term toxicity.
Arya LS 2006 Hodgkins disease in children	Previously untreated patients 4cycles of COPP alternating with 4 cycles of ABVD	Chemotherapy alone with alternating COPP/ABVD, without additional radiotherapy, provides high rates of durable remission a
Chastagner, P 2006 Glioma in children	Following surgery, patients received a combination of BCNU + cisplatin + VP16 (BCV), over 3 consecutive days.	The regime lacks efficacy and has unacceptable toxicity
Jacquillat CL 1975 Hodgkin's disease	Not previously treated One group - vincristine, chlormethine, procarbazine and prednisone (protocol H2-65) for six months, followed by monthly vinblastine injections. Additional prophylactic radiotherapy was given to 50 non-randomised patients.	Among 109 patients in stage III complete remission occurred in 53%
Diehl V 1998 Hodgkins disease	Group 1 Standard bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) scheme Group 2 - escalated dose BEACOPP Group 3 - cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) /doxorubicin, bleomycin, vinblastine, and	Combined with local irradiation, BEACOPP in one or both variants shows superior disease control compared with COPP/ABVD, with acceptable acute toxicity.

	dacarbazine (ABVD).	
Seiber M 2004 Hodgekins disease	Group 1 COPP/ABV/IMEP cyclophosphamide-vincristine-procarbazine-prednisone-doxorubicin-bleomycin-vinblastine-ifosfamide-methotrexate-etoposide) (CAI) Group 2 COPP/ABVD (COPP/ABV, dacarbacine) (CA)	CAI did not give superior results when compared with the standard CA in advanced-stage HD.
Myer RM 2005 Clinical stage I to IIA Hodgkin's lymphoma	randomized trial comparing ABVD alone with treatment that includes radiation therapy Stratified into favorable and unfavorable risk cohorts. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined-modality therapy if unfavorable risk. Patients allocated to ABVD received four to six treatment cycles.	5-year freedom from disease progression is superior in patients allocated to radiation therapy (P = .006; 93% v 87%); no differences in event-free survival (P = .06; 88% v 86%) or overall survival (P = .4; 94% v 96%)

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