

The role of mitomycin in the treatment of non-small cell lung cancer: a systematic review with meta-analysis of the literature

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Summary In order to clarify the role of mitomycin (MMC) in the treatment of NSCLC, we performed a systematic review of the literature and qualitatively assessed the selected studies using the ELCWP and Chalmers scales. 5 trials (202 patients) assessed the activity of MMC as single-agent chemotherapy in NSCLC. The overall response rate was 25% (95% CI 19–31). In 10 randomized phase III trials (1769 patients), we studied the role of MMC in combination therapy. A meta-analysis, based on the available published data, failed to show any survival advantage of the MMC containing regimens (hazard ratio = 0.95; 95% CI 0.83–1.10). Finally, 4 eligible trials (139 patients) assessed the activity of MMC regimens as salvage therapy, 3 in combination with vindesine and one with cisplatin and vinblastine. The overall response rate for the MMC-vindesine regimen was 10.5% (95% CI 1.7–19.4). In conclusion, MMC is an active drug for NSCLC but does not improve survival when combined with other active drugs, particularly cisplatin. Its use for salvage therapy appears to be associated with marginal activity only. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

Keywords: mitomycin; non-small cell lung cancer; meta-analysis; systematic review; chemotherapy

In the 1990s, chemotherapy has been shown able to improve survival of patients presenting with advanced non-small cell lung cancer (NSCLC, 1995). The survival benefit was obtained with first-generation active cytostatic agents – mainly ifosfamide, vinblastine, vindesine, mitomycin (MMC) – in combination with cisplatin (Donnadieu et al, 1991). New active drugs – the second generation – have appeared during the last decade, including gemcitabine, paclitaxel, docetaxel, vinorelbine and irinotecan. Their role in addition or in place of the first-generation agents, which should not be considered as obsolete for the unique reason that they are older and less fashionable, has yet to be defined (Meert et al, 1999).

In this context, we have performed a systemic review of the literature about the role of one of the first-generation drugs, mitomycin (MMC), in the management of NSCLC. In order to determine if it is worthy to further conduct trials with that agent, we have searched answers to the 3 following questions: (1) is MMC an active drug against NSCLC? (2) does MMC improve the results when added to other active agents? (3) is MMC useful for salvage therapy? We have performed this investigation by using a methodology similar to that we have already used to conduct evidence-based medicine analyses of the literature.

MATERIAL AND METHODS

To be eligible for the systematic review, a trial had to fulfil the following criteria: to deal only with NSCLC, to have been published as a full paper in the English or French language, to

have a prospective design and to assess the effect of MMC in a randomized trial or in a first-line or second-line phase II trial according to the studied question.

Trials were identified by an electronic search (Medline) in addition to the use of the personal bibliography of one of the authors and by consulting the references reported in the selected articles.

Each trial was read and assessed for methodology by 12 investigators, including 11 physicians and 1 biostatistician. Each investigator independently extracted the data from the articles and disagreements were resolved by consensus. Randomized trials were evaluated for methodology by 2 quality scores calculated on the basis of the data reported in the publications: the score proposed by Chalmers et al (1981) and used by Marino in two meta-analyses (Marino et al, 1994, 1995); and the score proposed by the ELCWP (European Lung Cancer Working Party) (Mascaux et al, 2000). Phase II trials were assessed by the ELCWP score for phase II studies (Meert et al, 1999).

The result of a phase III trial was considered as conclusive if the *P* value for the statistical test comparing the survival distributions between arms for the overall patients populations was <0.05 in favour of the experimental arm. The trial was then called 'positive'. In the other situations (statistically significant survival benefit for the control arm or non-statistically significant difference in survival distributions), it was called 'negative'.

The association between the quality scores or between a quality score treated as continuous variable and another continuous variable was measured by the Spearman ranks correlation coefficient. Its significance was assessed by testing a null hypothesis of equality to zero of this coefficient. The comparison between quality scores according to the value of a discrete variable was made by non-parametric Mann–Whitney (for dichotomic variables) or Kruskal–Wallis (for nominal variables with multiple classes) tests. To compare regimens according to the drug dose-intensity, we used the theoretical dose-intensity for the drug

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(reported in mg/m²/week) by dividing the theoretical absolute dose administered by the theoretical duration of the treatment before response evaluation (if not reported, we made the calculations with 3 cycles of treatment).

Confidence intervals (CI) for the response rate to the chemotherapy regimen were, for consistency, recalculated using the exact binomial distribution.

For objective response, the numbers of eligible and assessable patients were recorded in each article as described by the authors.

For the quantitative aggregation of the antitumoral response results and the reported toxic deaths, we measured the treatment effects using the odds ratios calculated on the contingency tables observed in each trials. The individual odds ratios were combined using the Peto method after having tested the homogeneity of the odds ratios estimated in each study.

For the quantitative aggregation of the survival results reported in the randomised phase III trials, we measured the treatment effect by the hazard ratio (HR) between the survival distributions. For each trial, this HR was estimated by a method depending on the results provided in the publications. The most accurate method consisted to calculate the estimated HR and its standard error using 2 of the following parameters: the HR point estimate, the log-rank statistic or its *P* value, the O-E statistic (difference between numbers of observed and expected events) or its variance. If not available, we looked for the total number of events and the log-rank statistic or its *P* value allowing calculation of an approximation of the HR estimate. Finally, if it was impossible to apply the second method, we extracted from the graphical representation of the survival distributions survival rates at some specified times chosen on a trial by trial basis in order to reconstruct the log-rank statistic and its variance. The individual HR point estimates were combined after acceptance of the null hypothesis of the homogeneity of the treatment effect across the various trials, using the Peto method in order to obtain a global HR estimate of the treatment effect. By convention, a HR < 1 implied a survival benefit for the experimental arm.

All reported *P* values are two-tailed.

RESULTS

A total of 19 trials were found to be eligible for the present systematic review: 5 phase II trials assessing MMC as first-line single-agent therapy, 10 phase III randomized trials assessing the addition of MMC to a basic active regimen and 4 phase II trials assessing the role of MMC-containing regimens as second-line chemotherapy for advanced NSCLC.

Question 1: is MMC an active drug against NSCLC?

5 studies (Israel et al, 1975; Samson et al, 1978; Ruckdeschel et al, 1981; Niell et al, 1989; Veeder et al, 1992a) including 202 assessable patients provided results about the activity of MMC when given as first-line single-agent therapy. Their design is phase II for 3 and randomized phase III for 2. 3 specifically deal with squamous cell carcinoma and one with adenocarcinoma and large cell carcinoma. Their main characteristics and results are shown in Table 1.

The global quality score ranged between 26.1% and 81.9% with a median of 57.3%. There was a good correlation between the score and the year of publication ($r = 1$) while no significant correlation was found with the number of eligible patients ($r = 0.6$; $P = 0.55$).

The reported response rates ranged from 19 to 50%, with an overall response rate of 25% (95% CI: 19–32%).

Question 2: does MMC improve the results when added to other active agents?

10 randomized trials comparing a basic chemotherapy regimen with or without MMC (Einhorn et al, 1986; Crino et al, 1988, 1990; Bonomi et al, 1989, Luedke et al, 1990; Fukuoka et al, 1991; Shinkai et al, 1991; Weick et al, 1991; Mylonakis et al, 1992; Gandara et al, 1993; Masutani et al, 1996) were available for a meta-analysis. Their main characteristics and results are summarized in Table 2 8 of them included more than 2 arms but we considered only the 2 arms of interest, leading to a total of 1769 eligible patients, 876 treated in the experimental arm with MMC and 893 in the control arm without MMC. As shown in Table 2, most often the data were missing to consider the number of randomized patients for the aggregation. The basic chemotherapy regimen was cisplatin–vindesine in 4 trials, cisplatin–vinblastine in 3 and cisplatin–etoposide, cisplatin or vindesine in 1 each. In 7 trials, a reduction of the dosage of at least one of the basic drugs was performed in the MMC arm. Significant improvement of response rate was reported in 3 trials but none was associated with significant survival improvement. All the trials were thus considered as negative.

The quality scores of the randomized trials are reported in Table 3. The ELCWP score ranged from 52.8% to 86.8% with a median of 66.5% and the Chalmers one from 30.6% to 64.8% with a median of 43.5%. There was a significant correlation between both scales ($r = 0.68$; $P = 0.03$). We found no significant correlation between the scores and the number of eligible patients included into the study, the date of study activation or the date of publication.

Table 1 Characteristics and results of the studies assessing the role of MMC as first-line single-agent therapy

Reference	n assessable patients	MMC DI (mg/m ² /wk)	OR (%) 95% CI (%)	ELCWP IV (%)	ELCWP EV (%)	ELCWP QS (%)
Israel et al, 1975	20	0.02 mg/kg	10 (50%) 26% – 74%	22.2	28.9	26.1
Samson et al, 1978	37	2.78	7 (20%) 5% – 33%	50	36.5	42
Ruckdeschel et al, 1981	28	6.67	5 (19%) 2% – 34%	50	61.7	57.3
Niell et al, 1989	53	2.5	10 (19%) 7% – 30%	69.4	70.7	70.2
Veeder et al, 1992b	64	2.78	19 (30%) 18% – 42%	83.3	81	81.9
Overall	202		51 (25.2%) 19% – 32%			

MMC: mitomycin C, DI: dose-intensity (mg/m²/wk), OR: objective response; IV: internal validity; EV: external validity; QS: quality score.

Table 2 Characteristics and reported results of the randomized studies assessing the role of the addition of MMC to a basic regimen

Reference	<i>n</i> eligible patients (<i>n</i> randomized)		Basic chemotherapy regimen	OR rate (%)			MS time (wks)		
	MMC arm	Control arm		MMC arm	Control arm	<i>P</i>	MMC arm	Control arm	<i>P</i>
Einhorn et al, 1986	41 (?)	41 (?)	CDDP-VDS*	20	27	NS	17	26	NS
Crino et al, 1990	57 (?)	69 (?)	CDDP-VP16	26	30	NS	37	35	NS
Bonomi et al, 1989	176 (?)	175 (?)	CDDP-VBL*	20	13	S	23	25	NS
Luedke et al, 1990	143 (?)	141 (?)	VDS*	27	<1	S	20	15	NS
Fukuoka et al, 1991	68 (69)	67 (68)	CDDP-VDS*	43	33	NS	42	50	NS
Shinkai et al, 1991	61 (62)	63 (64)	CDDP-VDS*	35	23	NS	45	39	NS
Weick et al, 1991	134 (139)	142 (156)	CDDP-VBL*	24	17	NS	25	21	NS
Mylonakis et al, 1992	51 (51)	52 (52)	CDDP-VBL	18	31	NS	32	35	NS
Gandam et al, 1993	110 (?)	108 (?)	CDDP	27	14	S	54	40	NS
Masutani et al, 1996	35 (?)	35 (?)	CDDP-VDS*	43	29	NS	33	36	NS

OR: objective response; MS: median survival; S: significant; NS: non significant; CDDP: cisplatin; VDS: vindesine; VBL: vinblastine; * = with reduction of the dosage of the basic drugs in the MMC-experimental arm.

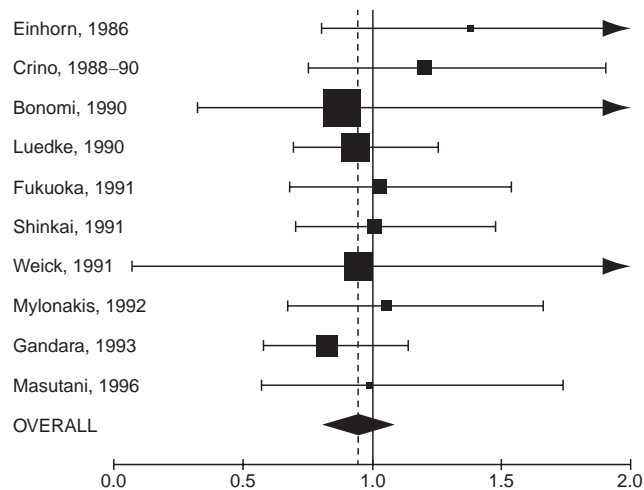


Figure 1 Results of the survival meta-analysis of the 10 randomized trials comparing a chemotherapy regimen with or without MMC

No significant bias being found in quality scores between the trials, a meta-analysis of survival and response results was performed.

For survival, the individual HR were calculated by one of the methods reported in the Material and methods section. In one case, the HR was estimated using the total number of events and the log-rank statistic, in 7 using extracted survival rates from the graphical representations of the survival distributions and in 2 using the global number of events in each arm. We aggregated firstly all the trials and secondly a subgroup of the 3 trials that respected the same drug dosage in the 2 arms. These meta-analyses failed to show a significant difference between the regimens with or without MMC. The individual and pooled hazard ratios (HR) are shown in Figures 1 and 2. The aggregation of the 10 randomized trials resulted in an overall HR of 0.95 (95% confidence interval or CI: 0.83–1.10) while the pooled HR for the 3 trials subgroup was 1.05 (95% CI: 0.83–1.33). The test for heterogeneity of the treatment effect was not significant ($P = 0.93$).

For response, the analysis had to deal with heterogeneity of the effect of the addition of MMC mainly due to the study of Luedke et al (1990) who compared vindesine with or without MMC.

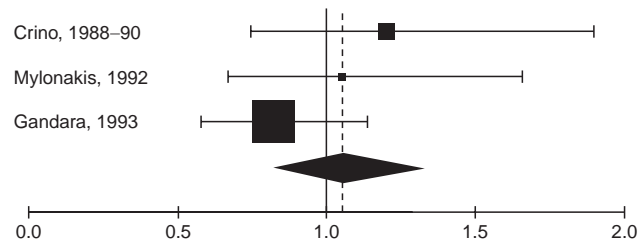


Figure 2 Results of the survival meta-analysis of the subgroup of 3 trials comparing a chemotherapy regimen with or without MMC, without drug dosage reduction

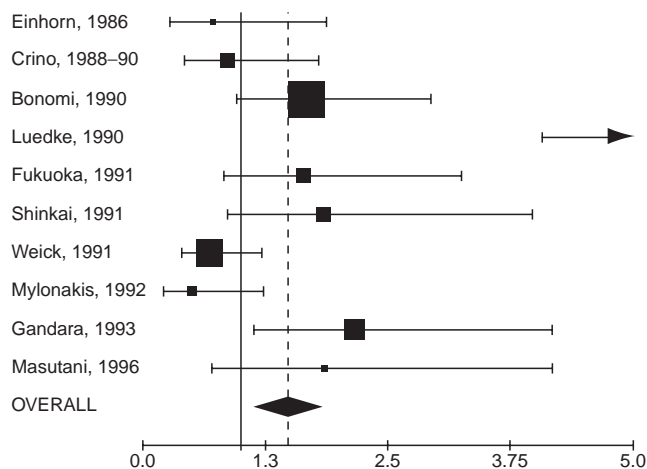


Figure 3 Results of the objective response rate meta-analysis of the 10 randomized trials comparing a chemotherapy regimen with or without MMC

As shown in Figures 3 and 4, when this study is included, a significant odds-ratio (OR) was obtained in favour of MMC-containing regimens: 1.48 (95% CI 1.17–1.86); when it is excluded, the OR (test for heterogeneity: $P = 0.54$) is not anymore significantly associated with an improved response rate: 1.21 (95% CI 0.95–1.54).

The number of observed toxic deaths was not significantly different between the arms with or without MMC, with an OR of 1.55 (95% CI: 0.73–3.28; $P = 0.98$; test for heterogeneity: $P = 0.53$).

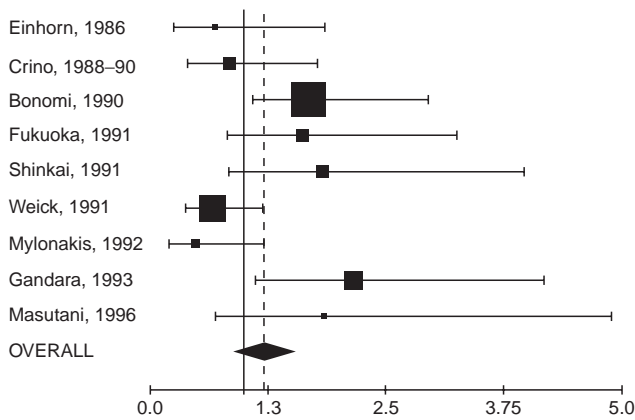


Figure 4 Results of the objective response rate meta-analysis of the randomized trials after exclusion of the study by Luedke et al (1990)

Question 3: is MMC useful for salvage therapy?

On the 4 prospective phase II trials found in the literature (Table 4), 3 deal with a combination of MMC with vindesine (Kris et al, 1985; Sculier et al, 1986; Bonomi et al, 1989) and 1 with cisplatin and vinblastine (Gridelli et al, 1992). The ELCWP quality score for phase II trials ranged from 21.1% to 75% with a median of 61.1%. The response rate ranged for the MMC-vindesine regimen from 0% to 17%, with an overall response rate of 10.5% (95% CI: 1.7–19.4%). It was 6% for the cisplatin-vinblastine-MMC combination.

DISCUSSION

Our systematic review intended to answer 3 questions about the role of mitomycin in the management of advanced NSCLC. A response to 2 of them is possible: MMC is an active drug for this disease as shown by the phase II trials testing its activity as single-agent first-line chemotherapy and the meta-analysis of the randomized trials fails to obtain any survival advantage when MMC is added to a basic combination regimen with first-generation cytostatic agents (mainly cisplatin and/or vinca alkaloids). For the last question concerning the role of the drug for salvage chemotherapy, the response is less evident because of the limited number of published studies on the topic.

To perform our systematic review, we have used a methodology that was similar to prior studies of this type reported by our Group. The principle is to assess the trial quality by methodological scales

– the Chalmers and ELCWP scores – in order to search for potential methodological aspects of the published trials that might explain heterogeneity of the reported treatment effects. If there is no significant difference among the publications, as in the present report, we go further in our analysis and perform a quantitative aggregation (meta-analysis) of the results of the individual trials. This approach applied to MMC in advanced NSCLC was relatively easy because all the trials provide similar results. All the phase II studies assessing the role of MMC as first-line single-agent therapy revealed that the drug is active and none of the randomized studies assessing the role of the addition of MMC to a basic regimen showed a survival advantage for the experimental arm. We had thus not to compare for quality 'positive' and 'negative' studies. The only significant finding was an improved quality in favour of more recently published phase II trials, which can be very well explained by the amelioration of the trials methodology obtained over the 3 last decades.

Mitomycin is associated with a 25% objective response rate when administered as single-agent first-line chemotherapy in advanced NSCLC. Most of the authors consider that the cut-off to consider a drug as active in this disease is defined by the observation of response rates above 15 to 20%. The results reported by the 5 trials described in Table 1 are consistent, despite being conducted over a relatively long period (~25 years). Some of them were performed with some specific histological subtypes of NSCLC but we do not believe that this heterogeneity is a potential source of bias. The meta-analysis that we performed about response in NSCLC failed to show significantly different effects according to the histological type.

The next step of the systematic review was to identify the potential benefit for the patient of the inclusion of MMC in the chemotherapy treatment. The primary endpoint that we choose was survival, the endpoint usually used by the investigators for phase III randomized trials. Other endpoints that could be of interest for the patients are symptom control, quality of life or toxicity of the treatment but the publications reported no data or too poorly described data to allow a meaningful aggregation. The main problem in the interpretation of the results of our meta-analysis is, in 7 of the 10 randomized trials, a dosage reduction of the non-MMC drugs in the experimental arm compared to control arm. For this reason, as shown in Figures 1 and 2, we performed two meta-analyses, one with all the studies and another with the 3 studies with the purest design to address our question. None revealed a survival advantage for MMC-regimens but due to the small number of adequately designed randomized trials

Table 3 Quality scores of the randomized studies assessing the role of the addition of MMC to a basic regimen

Reference	Chalmers score %			ELCWP score %		
	Internal validity	External validity	Total	Protocol design	Performance analysis	Total
Einhorn, 1986	50	18	40.9	61.9	50	54.8
Crino, 1988/90	28.6	36	30.6	66.7	66.1	66.4
Bonomi, 1990	38.1	12	30.6	50	54.8	52.9
Luedke, 1990	38.1	30	35.8	52.4	53.1	52.8
Fukuoka, 1991	57.1	48	54.6	90.5	71.9	79.3
Shinkai, 1991	71.4	48	64.8	85.7	87.5	86.8
Weick, 1991	47.6	42	46	61.9	73.4	68.9
Mylonakis, 1992	47.6	48	47.7	73.8	53.1	61.3
Gandara, 1993	47.6	48	47.7	59.5	71.7	66.7
Masutani, 1996	38.1	42	39.2	61.9	74.2	69.2

Table 4 Characteristics and results of the studies assessing the role of MMC-containing regimens as second-line chemotherapy

Reference	n assessable patients	Other drugs of the regimen	MMC DI	OR (%) 95% CI	ELCWP IV (%)	ELCWP EV (%)	ELCWP QS (%)
Kris et al, 1985	29	VDS	2.5	5(17%) 2–33%	72.2	57.7	63.6
Sculier et al, 1986	16	VDS	2.5	1 (6%) 0–21%	75	75	75
Bonomi et al, 1989	88	CDDP + VBL	3.3	5(6%) 0–11%	22.2	20.4	21.1
Gridelli et al, 1992	12	VDS	2.5	0	44.4	63.7	58.5

MMC: mitomycin C, DI: dose-intensity (mg/m²/wk), OR: objective response; IV: internal validity; EV: external validity; QS: quality score; VDS: vindesine; CDDP: cisplatin; VBL: vinblastine.

(only 3), the provided evidence might not be sufficient to change practice.

Although of less interest, we aggregated also the response rates. We had to deal in the analysis with a heterogeneity problem because of the trial of Luedke et al (1990) who reported in a very large trial a very significantly improved response rate when MMC was added to vindesine but without significant effect on survival. This trial may be criticized because the response rate obtained for vindesine was very low and is thus not in agreement with the majority of the other studies published with this drug in the literature. When this trial is omitted for meta-analysis (Figure 4), there is no response rate improvement by the addition of MMC while when it is included (Figure 3), there is a positive advantage in favour of MMC-containing chemotherapy.

The last point that we analysed was the role of MMC in salvage chemotherapy regimens (Table 4). In fact, the only regimen that has been the topic of publications is MMC–vindesine. The response rate reported is around 10%, which is rather marginal. In fact, we believe that the available literature for this question has to be considered as non-conclusive because of a lack of sufficient data, including about first-line chemotherapy characteristics.

In conclusion, the present systematic review shows that MMC is an active drug against advanced NSCLC but does not improve survival when added to other first-generation active cytostatic agents like cisplatin, vindesine and vinblastine. It should not be anymore used in this indication. Nevertheless its role for salvage chemotherapy or in combination with the second-generation active drugs require to be studied in further investigations.

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