INTRODUCTION

It has been 25 years since a review of mitomycin C (MMC) was published in Cancer Treatment Reviews (1). Thus it seemed appropriate to determine what the clinical impact of MMC has been during that time and to assess its probable future role in the treatment of several major neoplastic diseases in which it has been used in the past. Mitomycin C is marketed in most countries worldwide. In the U.S.A. the new drug application (NDA) for MMC was approved by the Food and Drug Administration (FDA) in 1974. In the summer of 1975 a meeting was held by the recently formed FDA Oncology Advisory Committee which retrospectively reviewed the approved NDA for MMC and had serious concerns about clinical data in the filing. The original NDA included usefulness in the treatment of cancers of the head and neck, lungs, breast, cervix, colon and rectum, hepatic cell carcinoma and melanoma in addition to stomach and pancreatic cancer (2). Three particular concerns of the Advisory Committee were that although data on about 1000 patients were included there was little consistency in the doses and regimens used for any one disease category, the recommended Dosage and Administration was obsolete, and the cut-off for treatment was a platelet count of 75 000/mm³ which was considered too low.

Revised labelling was submitted by the sponsor, Bristol Laboratories (a former pharmaceutical division of Bristol-Myers Squibb), which included a more modern well-spaced bolus dosing regimen and a minimum platelet count of 100 000/mm³. After discussion between FDA staff, consultants to Bristol Laboratories and advisory committee members, the above modifications, along with a limitation on indications for stomach and pancreatic cancer only, were incorporated into the labelling. These remain the only indications in the U.S.A. for MMC to this day (3). Nevertheless, off-label use in many other diseases has continued. Mitomycin C was briefly reviewed by Doll et al. in 1985 (4) who recognized its utility in superficial bladder cancer, but suggested investigational use only in other diseases because of its toxicity profile.

This update of MMC will discuss what has happened in clinical usage by disease type, and include a brief review of toxicity. A major text book has provided background information (5). Literature over the last 25 years was retrieved by MEDLINE search and from publication bibliographies. Data tabulations include only clinical trials with 10 or more patients. Individual case reports are avoided unless cogent information is presented. Objective response
data will be the main emphasis because it has been more consistently reported over time, but it should be noted that survival time and quality of life are far more important therapeutic benefits and have been recognized as such for registrational approval (6). In order to identify possible trends in therapeutic outcome, response results in some instances have been averaged. These findings should be interpreted with caution because such historical data tend to be highly heterogeneous.

**BLADDER CANCER**

Single agent activity of MMC given parenterally for metastatic transitional cell carcinoma (TCC) has been noted with a response rate of 33% among 75 patients (7). Combinations of MMC with other agents however, seemed to increase toxicity without increasing efficacy (8). A recent report on the combination of MMC + 5-fluorouracil (5-FU) and radiation noted substantial local control in elderly patients (9).

The broadest use of MMC in bladder cancer has been in the intravesical treatment of various stages of transitional cell carcinoma (TCC) and carcinoma in situ (CIS). In patients not amenable to transurethral resection (TUR), MMC given intravesically at doses ranging from 20 to 60 mg gave a complete response (CR) rate of 21/43 (49%) (10). In one study, MMC therapy was compared to no treatment post-TUR in 54 and 31 patients, respectively (11). At an average of 34 months, 11.1% had recurrent tumors among the MMC treated group compared to 54.8% among those receiving no treatment. The activity of MMC was confirmed in treatment of low stage tumors occurring in patients in France (12), England (13), Italy (14), Hungary (15) and Germany (16). Among 117 patients failing thiotepa, 43 (37%) had negative cytology following MMC therapy (17). Durable responses of CIS to MMC treatment have been observed in Australia, Japan and the Netherlands (18, 19, 20). A trial of 30 min versus 60 min in dwelling times of MMC significantly favoured the longer time in preventing recurrence (21).

There have been a number of reports comparing the efficacy of MMC with doxorubicin in the topical treatment of bladder cancer. In a study performed in Finland, the two drugs were found to be equivalent in the treatment of CIS (22). This group used phosphate-buffered MMC and methylprednisolone to relieve bladder irritation. In a similar study of Ta and T1 tumours, MMC was found to be significantly superior to doxorubicin in CR rate (85% vs 47% respectively) and in disease-free interval (23). An abstract from Italy comparing the same two drugs in 102 patients concluded that local therapy with MMC gave better results than doxorubicin in single or unifocal superficial bladder neoplasms (24).

The introduction of bacillus Calmette-Guérin (BCG), approved in the U.S.A. for the treatment of CIS, established the principle of local bladder cancer treatment based on the apparent high response rate to BCG therapy (3). This was supported by a comparative trial of BCG vs doxorubicin in which the CR rate for BCG was significantly higher than doxorubicin (25). Such a difference has not been demonstrated in comparisons of MMC and BCG, particularly on long term follow-up. Two major studies involving 261 patients in Norway (26) and 344 patients in the Netherlands (27) determined there was no difference between MMC and BCG therapy for tumour progression or patient survival with a trend favouring BCG for CIS treatment and MMC for non-CIS disease. An important observation in the Norwegian study was that cross-over treatment was successful with 39% of patients responding to second line with BCG and 19% to second line MMC suggesting that MMC is best given first.

Recently a group at Ohio State University has applied several pharmacokinetic (PK) interventions to improve exposure to MMC treatment of bladder cancer. These include increasing the dose (40 mg instead of 20 mg which is common in the U.S.A.), reducing dosing volume, ultrasound-guided bladder emptying, voluntary dehydration and urine alkalinization. These PK interventions reduced residual urine volume and urine production rate, and increased the area-under-concentration-time profile (CXT) as predicted (28). In a randomized multicentre Phase III trial of 217 high risk patients (29), those in the PK optimized arm showed significantly longer time to recurrence and a greater proportion free of recurrence than patients in the standard arm (18.1 vs 11.4 months and 39% vs 21% p = 0.007).

**Summary**

Although MMC is active as a single agent in metastatic bladder cancer it is not likely to be used in the future considering the impact of newer agents such as gemcitabine and taxoids (30, 31). For local intravesical treatment of early stage disease MMC is possibly the most active cytotoxic drug available. Recently reported long-term follow-up data suggest that MMC rivals BCG in outcome and may be superior in non-CIS disease with BCG remaining the treatment choice for CIS. This may be influenced in the future by the information on sequence and by application of newer delivery regimens such as the one devised at Ohio State.
Three major reviews on the use of MMC in breast cancer were published in 1985 (32, 33, 34), and two shorter reviews appearing in 1988 (35, 36). All of these preceded the marketing of paclitaxel and vinorelbine, and more numerous clinical trials of various high dose chemotherapy/rescue strategies. Each of the five articles made one or more of the following points:

(i) Mitomycin C as a single agent was continually found to be active both first line and second line in therapy of advanced breast cancer including patients who had undergone prior chemotherapy;
(ii) The activity of MMC was modestly enhanced in combination with other agents, particularly anthracycline-type agents and vinca alkaloids;
(iii) Because of its cumulative myelosuppression, the use of MMC first line and for adjuvant use was not recommended;
(iv) There was the impression that when MMC was given with care to certain patients the side-effect profile was milder than other therapies and the quality of life was superior even if responses were short-lived.

The single agent activity of MMC in breast cancer was reaffirmed 10 years ago by Walters et al. (37) in a trial of two dose schedules of MMC in patients who had been pretreated at varying times. One group received 20 mg/M² on day one and every 6 weeks thereafter (standard dose, SD); the second group received the same starting dose but was subsequently treated with 5 mg/M² every 6 weeks (low dose, LD). Response rate, time to progression (TTP) and median survival time (MST) were all comparable with less intense haematologic toxicity observed in the LD group. Activity of MMC (12 mg/M² every 6 weeks) was also seen in a comparative trial versus paclitaxel (38) but with a partial response (PR) rate of only 6%. The dose intensity of MMC in this study may have been low since others using MMC in the 10 to 12 mg/M² range usually administer it every 28 days (see subsequent reports).

Studies of vinblastine + MMC have continued with varying outcomes in advanced breast cancer. Four reports are summarized in Table 1. The best results shown (from reference 40) were with the highest doses of both drugs (vinblastine 7 mg/M²; other studies 6 or 5 mg/M²). Similar results have been reported with MMC combinations involving vinodesine (43, 44, 45). The new vinca vinorelbine has been shown to have single-agent effectiveness in advanced breast cancer with an objective response rate (ORR) averaging 33% in 378 patients from seven studies (46, 47, 48, 49, 50, 51, 52). A similar calculation for the combination of vinorelbine + MMC gave an ORR of 45% in 321 patients (53, 54, 55, 56, 57, 58, 59). These results suggest a trend for higher response using this combination. However, the impact of adding MMC to vinorelbine treatment on survival parameters and quality of life was unclear.

The anthracenedione drug mitoxantrone, which is approved in the U.S.A. for treatment of advanced prostate cancer and acute non-lymphocytic leukaemia (3), has been used in combination with MMC +/- methotrexate, in both advanced untreated breast cancer (60, 61, 62) and second line after primary or adjuvant chemotherapy (63, 64). Modest responses were seen in both settings, with the impression of milder toxicity compared to anthracycline containing regimens. In one report, addition of filgrastim to the three drug combination contributed to prolonged survival (65).

In England, a first line treatment of advanced breast cancer has been developed called FILM (5-FU, ifosfamide, leucovorin and MMC). Initial total response was 83% (CR + PR) among 24 patients. A group of 80 patients could be assessed at 5 years and 56 (70%) remained in remission and 69 (86%) were still alive (67). In a recent phase II study reported from Japan a single high dose of MMC added to CMF was found to enhance relapse free survival in the adjuvant treatment of premenopausal patients (68).

<table>
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<th>Reference</th>
<th>No. patients</th>
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<td>44</td>
<td>10</td>
<td>Q 4 wks</td>
<td>10 (23)</td>
</tr>
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<td>40</td>
<td>34</td>
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<td>189</td>
<td>12</td>
<td>Q 6 wks</td>
<td>22 (11.6)</td>
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</tbody>
</table>
Summary

The limited single agent activity of MMC against breast cancer has been repeatedly confirmed. There is continuing evidence that MMC in a combination which includes a vinca alkaloid is a useful and well-tolerated palliative treatment in advanced breast cancer in the second or third line setting. A likely target population would be patients for whom anthracyclines are medically contraindicated or those with disease resistant to these agents. One combination involving ifosfamide has shown utility first line. The relationship of MMC containing regimens to treatment with taxoids remains to be defined.

CERVIX CANCER

There have been few recent publications about the use of MMC as single agent in this disease. In one study a dose intense course (75 mg/M² total) as post-surgical adjuvant treatment contributed to a disease-free median survival at 29 months of 87.5% (69). In a phase II trial, MMC gave 6/52 (12%) responses among evaluable patients (70). The dose schedule was 20 mg/M² every 6 weeks. Much attention was drawn to the paper by Miyamoto et al. which used sequential bleomycin followed by MMC in advanced cervical cancer and noted 14/15 (93%) patients with an objective response (71). Six subsequent studies tried to duplicate these results (72, 73, 74, 75, 76, 77), but the total response rate for all the studies was 34/125 (27% range 9–40%). Addition of vincristine to bleomycin + MMC was found to be effective in treating advanced cervical cancer in one study (78), but was not recommended for second line treatment in two further reports (79, 80). The combination of MMC + cisplatin (DDP) has been used in non-resectable residual disease and gave objective responses in 35% of the patients in one study (81) and 60% in another where large doses of MMC were used 30 mg/M² every 4 weeks (82). This combination has also been used as primary chemotherapy to reduce bulky disease prior to surgery with 13/17 (76.5%) patients responding leading to two pathological complete responses after surgery (83).

The triple combination MMC + vincristine or vindesine + DDP has given high response rates (56–75%) in the treatment of advanced disease (84, 85). These drugs have also been used for intraarterial primary treatment of bulky disease (86, 87). In one trial (87), two doses of cisplatin were compared (50 vs 75 mg/M²). The higher dose was significantly more active in achieving CR than the lower dose. The four drugs MMC + vincristine + DDP + bleomycin (or its derivative peplomycin) have been used in advanced disease with similar results, the overall response from five studies being 103/150 [68.7%, range 47–77%] (88, 89, 90, 91, 92). This regimen seemed beneficial when used prior to surgery (93), but outcome was inconsistent when used before radiation (94, 95, 96).

Summary

Mitomycin C together with a vinca or cisplatin appears to give high response rates in advanced cervical cancer. However, the role of MMC in these combinations is unclear. More recently ifosfamide, which is one of the most active drugs, has demonstrated high response rates in combination with platinum products (5). Whether or not ifosfamide is superior to MMC in this disease remains to be determined.

COLORECTAL AND ANAL CANCER

Mitomycin C has been tested clinically within the last 25 years as a single agent in several ways. Given as either a bolus injection (97, 98) or a prolonged infusion (99, 100) the cumulative response in these four trials was 6/132 (4.5%). When the anti-glycolysis agent lonidamine (101) was given with MMC (102, 103), the total objective response rate was 2/43 (4.7%). A common combination, tried mostly in advanced colon carcinoma, was 5-FU + MMC. The cumulative result of seven reports gives 103/380 (28% range: 17–53%) objective responses (104, 105, 106, 107, 108, 109, 110). In all cases the 5-FU was given by infusion for 24 or more hours. In one report (108), the combination was compared with 5-FU alone and gave 52/98 (53%) responses vs 36/97 (37%) for 5-FU alone. Thus there is the suggestion that MMC may add to the response, but this is not so for survival.

Two major trials have reported encouraging results with 5-FU + MMC + radiotherapy (RT) in cancer of the anal canal. In one trial all patients were treated with RT and about half were given 5-FU + MMC (111). Local failure rate for RT alone at 42 months was 59% and for RT + chemotherapy was 36%. In another large study of similar design all 291 evaluable patients were given RT + 5-FU and about half were treated with MMC (112). Disease-free survival at 4 years was significantly higher in the MMC arm (73% vs 51%).

Regional chemotherapy of metastatic colorectal cancer has been under investigation for several years (113). Hepatic arterial infusion with MMC + floxuridine (114), 5-FU + Adriamycin + MMC (FAM) (115)
or 5-FU + MMC (116) have given fairly high response rates but the role of MMC is unclear. Mitomycin C alone has been used intra-arterially and given responses of 17% (117) and 20% (118). In studies of intraportal arterial infusion of either MMC alone (119) or MMC + 5-FU (120) for recurrent colorectal cancer, palliation with pain reduction was noted. Adjuvant portal liver infusion with 5-FU + MMC and surgery seemed to reduce recurrence rate compared with surgery alone in a group of 533 patients (121).

Summary

The single agent activity of MMC in colorectal cancer must be deemed minimal. In combination with 5-FU there are conflicting reports on whether or not MMC adds to the activity of 5-FU. Treatment of cancer of the anal canal with MMC + 5-FU + radiation has been successful in reducing the need for radical surgery. Mitomycin C combinations may have some role in palliative intra-arterial treatment of liver metastases. The recent introduction of the camptothecin irinotecan for second line treatment of colorectal cancer after 5-FU (3) and investigation of oxaliplatin for the same indication (122) has further diminished the role of MMC in treating colorectal cancer.

GASTRIC CANCER

In a review of the chemotherapy of gastric cancer Preusser et al. (123) noted the response to treatment with MMC as a single agent at 63/211 (30%). Of various combinations tried with MMC the most common was 5-FU + doxorubicin + MMC (FAM), first reported by MacDonald et al. (124), with 26/52 (42%) objective responses among patients with advanced gastric cancer. Preusser noted that in eight reported studies of the original FAM regimen, the response rate was 113/346 (33%) with median duration of 7 months and survival of 9 months. Several variants of FAM have given similar results. More recently Park et al. (125), reported a comparative trial of a modified FAM regimen (3 day infusion of 5-FU instead of bolus injection) vs palliative treatment only of gastric cancer. The proportion alive at 1 year was significantly greater among the treated patients compared to those receiving no therapy. Adding DDP to FAM (FAMP) gave 5/12 (42%) responses (126). Substituting DDP for 5-FU (PAM) gave comparable results to FAM in a comparative trial among 50 patients (127). Using the same drugs, but giving 5-FU by 5-day infusion yielded a 62.5% response rate with 7.2 months median survival (128). Substituting epirubicin for doxorubicin (FEM) gave higher responses in a phase III trial versus FAM, but no increase in survival (129). Other studies of FEM did not support its use (130, 131). A phase I/II study of MMC + irinotecan has given 5/10 responders so far (132), but a trial of UFT + MMC (with the MMC given at 5 mg/M² weekly) indicated inferiority of this combination compared 5-FU + DDP, or 5-FU alone (133). A small study conducted in Germany in pretreated patients used continuously infused MMC (120 h) at a dose of 20 mg/M² per 5-day course for a maximum of four courses (134); the response rate was 6/20 (30%). It was noteworthy that 5/8 patients responding followed 5-FU treatment and only 1/12 after receiving cisplatin/paclitaxel combinations.

Mitomycin C has a long history of use for the adjuvant treatment of gastric cancer. A trial reported in 1978 of 430 evaluable patients assigned either to surgery + MMC or to surgery alone found no difference in survival, but the subset of patients with moderately advanced lymphatic metastases or involvement of serosa had significantly improved survival at both 5 and 10 years (135). In two more recent reports of postoperative adjuvant treatment of gastric cancer an untreated control group was also included. In the first, MMC alone was used at 20 mg/M² every 6 weeks for four courses starting less than 6 weeks after surgery (136). At a median follow-up of 105 months 49/66 had died in the control arm compared to 40/68 in the treatment group. The actuarial survival curve was significant (p < 0.025) in favour of the treatment group. The second (137) used the FEM regimen, but with a lower dose of MMC per injection (10 mg/M²) and lower total dose (30 vs 80 mg/M²). Although there was a survival trend favouring therapy, it did not reach statistical significance. As a result the authors concluded that such treatments did not have a role in gastric cancer management. A comparison of MMC + fltoraflur vs MMC alone as adjuvant treatment showed a significantly greater 5-year survival for the combination over MMC alone (138). A randomized trial conducted in Spain compared MMC + tegafur vs no treatment following surgical resection of stage III gastric cancer (139). A single dose of 20 mg/M² MMC was given 28 days after surgery followed 30 days later by tegafur at 400 mg twice daily for 3 months. At a median follow-up of 37 months, the overall and disease-free survival were significantly higher among patients receiving chemotherapy compared to those who did not.

Summary

The activity of MMC in gastric cancer has been confirmed. The FAM regimen has been investigated...
extensively, although its utility was never firmly established. Recently the use of MMC has received less attention in treatment of gastric cancer with the advent of newer agents such as the taxoids (140, 141) and oxaliplatin (142). As with other diseases, if MMC is to have any place in the therapy of gastric cancer in the future it will need to be re-investigated in the context of these newer treatments.

HEAD AND NECK CANCER

The activity of MMC in squamous cell carcinoma was confirmed in a phase II trial in oesophageal cancer in which 10/24 (42%) of the patients treated had a partial response (143). Considerable haematologic toxicity was encountered, most likely associated with the high dose per course of MMC used (20 mg/M²). Mitomycin C was combined with RT for the treatment of squamous cell carcinoma of the head and neck on the hypothesis that MMC would inhibit hypoxic tumor cells which are resistant to radiation (144). Among 195 patients randomized to receive RT alone or with MMC, those on the combined treatment had a statistically significant benefit in cause specific survival, local recurrence free survival and local regional recurrence free survival; overall survival was not significantly different. In another study of the combination of RT with MMC continuous hyperfractionated accelerated radiotherapy was used with or without MMC (145). Of 123 patients, 62 received RT alone and 61 RT + MMC. Actuarial survival (Kaplin-Meier) was significantly improved among the combined treated patients as well as local tumor control thus corroborating the findings of the previous study (144).

Treatment of head and neck cancer with RT + 5-FU + MMC gave an initial high response rate with a CR of 27/44 (64%) (146). Later reports, however, in which patients were given RT with or without the same two drugs failed to show that chemotherapy added to the efficacy of RT alone (147, 148). The combination of DDP + 5-FU + MMC together with RT provided high response rates for local control, but were associated with severe mucositis in the majority of patients and haematologic toxicity in nearly half of the patients (149). A similar regimen with a lower dose of MMC (6 mg/M² vs 10 and 8 mg/M²) and without RT was used to treat advanced head and neck tumours and achieved a response rate of 73% (CR 5/56, 9%; PR 36/56, 64%). The regimen was stated to have good response duration and to be well-tolerated (150).

Another combination which has been used in conjunction with RT is MMC + bleomycin. Induction chemotherapy with this regimen gave a response rate of 44/56 (79%) which was improved further by subsequent RT (151). Toxicity was considerable with both skin (probably related to bleomycin) and connective tissue involvement in radiated areas possibly related to the regional arterial MMC. Zarotnik et al. treated head and neck cancer patients with RT +/– concurrent chemotherapy with MMC + bleomycin (152). The CR was 31% for RT alone and 59% for RT + chemotherapy with a similar benefit seen in survival parameters and with oropharyngeal carcinoma being the most responsive lesion.

A series of phase II trials carried out in metastatic and/or relapsing disease used varying drug combinations; some examples are depicted in Table 2. Addition of hydroxyurea to MMC + 5-FU resulted in low activity (154). All other combinations achieved objective responses above 50% with some complete responses being seen. The epirubicin (157) containing regimen was active, but considered very toxic (mainly haematologic). The combination of MMC + doxorubicin + DDP with 5-FU maintenance was designed to permit full dosing, but reduce mucositis (158). Response to the initial treatment was very high (94%) and permitted 27 patients to go on to 5-FU maintenance with a median duration of 38 weeks. Considerable myelosuppression was encountered.

Summary

Mitomycin C is clearly active against head and neck cancer as established by comparative clinical trials in
which either RT or other drugs were given with and without MMC. In most cases MMC appeared to add significantly to the efficacy of the regimen under study. Where MMC seemed to add the least was when multiple drugs were used, in which case its main contribution was to toxicity. The problem with this group of diseases is that there are no drug combinations which are considered standard. Thus the use of MMC in the treatment of head and neck cancer appears to be determined largely by the experience of the clinical investigators involved with research on this disease.

**NON-SMALL-CELL LUNG CANCER (NSCLC)**

Single agent activity of MMC was reported from France in 1975 with 10/20 (50%) of NSCLC patients responding on a weekly low-dose regimen (159). Samson *et al.* (160) treated advanced adenocarcinomas of the lung with MMC and obtained a response rate of 7/35 (20%). In a comparative trial published in 1992, Veeder *et al.* noted 19/64 (30%) patients with squamous cell lung carcinoma had partial responses to MMC alone given at 20 mg/M² for the first dose and at 15 mg/M² every 6 weeks thereafter (161). Although a wide variety of drug combinations including MMC have been tried in the treatment of NSCLC, the most important in the last two decades has been the three drugs known usually by the acronym MVP for MMC + Vinca alkaloid + Platinum (DDP). The majority have involved either vinblastine or vindesine and the results with vinblastine are shown in Table 3. Although the patient populations were similar in terms of advanced disease some had prior chemotherapy and some did not. Likewise various drug dosages were used, especially cisplatin which ranged from 40 to 120 mg/M². Mitomycin C was given every 3, 4 or 6 weeks. The 18 studies listed involving 1091 patients gave an overall response rate of 39%. The highest response rates were associated with high doses of DDP (= or > 100 mg/M², *p* < 0.0001). Patients who had received prior chemotherapy were more resistant than those who had not (*p* < 0.016). When comparisons were made between vinblastine + MMC and MVP using the same cisplatin dose, MVP tended to be superior in response, but not in survival. Most of the publications noted useful palliation in the form of symptomatic relief with MVP treatment.

In four reports of the two drug combination of MMC + vindesine the effect of prior chemotherapy was evident since 42/84 (48%) of patients without prior therapy responded compared with 6/53 (11%) with prior therapy (179, 180, 181, 182). A survey of 17 studies of MVP with vindesine (references 183–199) gave an overall response of 459/1290 (36%). The same trends were observed regarding cisplatin dose and prior chemotherapy as seen with vinblastine, but the significance was less marked. When two drug combinations were included for comparison,

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**Table 3** Mitomycin C + vinca alkaloid + platinum (MVP) regimen with vinblastine in the treatment of non-small cell lung cancer

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<th>Diagnosis</th>
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<th>DDP</th>
<th>Response number</th>
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<td>stage IIIB-IV</td>
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<td>8</td>
<td>50</td>
<td>38</td>
<td>118</td>
<td>32</td>
<td>177</td>
</tr>
<tr>
<td>stages IIIA-IIIB no rx</td>
<td>4.1 (av)</td>
<td>8</td>
<td>100</td>
<td>24</td>
<td>37</td>
<td>65</td>
<td>178</td>
</tr>
</tbody>
</table>

Totals – – – 451 1091 39 –

VLB, vinblastine; no rx, no prior chemotherapy indicated.
MVP tended to have a higher response rate, but conferred no improvement in survival. It was noteworthy that little mention was made of the palliative effects of this MVP regimen and considerable attention was paid to the severity of the toxicity involved. It should be noted that many of the MVP regimens are associated with considerable morbidity and even some deaths related to therapy which must be balanced against the possibility for useful palliation.

Many other drug combinations have been tried in advanced NSCLC, but none have consistently exceeded the two MVP regimens in response (5). A newer version of MVP consisting of MMC + vinorelbine + carboplatin + GM-CSF gave a response of 16/40 (40%) and was well-tolerated (200). A recent report from Japan which used vinorelbine in MVP obtained a response rate of 25/44 (57%) (201). Another combination which has often given responses exceeding 40% is MMC + ifosfamide + DDP (MIP) (202, 203, 204, 205), but in a randomized multicentre trial the response was under 10% (206). However, the introduction of gemcitabine and the taxoids and their inclusion in combinations with other drugs in many clinical trials has focused attention away from MVP/MIP regimens in the treatment of NSCLC. In a phase I/II trial the combination of MMC + gemcitabine + vinorelbine gave a response of 9/20 (45%) and was well tolerated (207). A recent review by Sweeney and Sandler of the chemotherapy of NSCLC has noted the modest improvement offered by newer agents (208).

Summary

Mitomycin C has confirmed single agent activity in NSCLC and an average response of 38% in MVP combinations involving over 2000 patients with advanced disease. The vinblastine containing version of MVP seems to be associated with significant palliation. However, the role of MMC in management of NSCLC will need to be redefined in light of newer agents.

PANCREATIC CANCER

Mitomycin C was originally reported (1) to have limited single agent activity in cancer of the pancreas. A number of publications report trials combining MMC with other cytotoxic drugs. Two combinations which gave initially promising results were streptozocin + MMC + 5-FU (SMF) and 5-FU + Adriamycin + MMC (FAM) (209, 210, 211). A randomized trial of 5-FU + MMC with or without streptozocin gave objective responses for SMF of 34% and the two drug combination of 8% (212). However, survival was the same for the two regimens. A group from Memorial Sloan-Kettering Cancer Centre achieved an 14% response rate with their version of FAM, but noted increased survival among responders (213).

Several large group studies were mounted to examine the efficacy of some of these combinations. Cullinan et al. compared 5-FU alone with 5-FU + Adriamycin (FA) and 5-FU + Adriamycin + MMC (FAM) and found no advantage for the combinations over 5-FU alone (214). Both the Cancer and Leukaemia Group B (215) and the Gastrointestinal Tumour Study Group (216) compared FAM and SMF prospectively. These trials failed to confirm initially reported response rates. In a small study of 22 patients, adding methylCCNU to 5-FU + MMC achieved a 40% response rate among evaluable patients (216). A phase III trial involving 187 patients compared 5-FU alone to combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine and MMC (called the Mallinson regimen) and to 5-FU + doxorubicin + cisplatin (FAP). Time to progression was the same in all three arms with the Mallinson regimen having a slight advantage in median survival (218). A combination of infused 5-FU + MMC + leucovorin + dipyridamole gave a response rate of 39% among 38 patients with an MST of 15.5 months in locally advanced pancreatic cancer (219). Finally, addition of MMC to treatment with gemcitabine gave a 46% response rate, higher than either agent alone, historically (220).

Summary

Although MMC has some single agent activity against pancreatic cancer, its contribution to the various combination therapies tested is unclear. As usual, promising results from small clinical trials are not realized in large multi-institutional clinical trials. Thus, the role of MMC in the treatment of pancreatic cancer still needs elucidation. More recently, the emergence of newer agents such as gemcitabine and rubitecan (9-nitrocamptothecin, 221) or cytostatic agents such as marimastat (222) has focused attention away from the use of MMC in this disease.

TOXICITY

The delayed cumulative myelosuppression caused by MMC has been known for a long time and led to widely spaced dosing strategies to permit recovery. It is the non-haematologic toxicities however, that have not only put limitations on MMC use but rendered unfeasible higher doses with haematopoietic
stem-cell support. These toxicities are included in the current U.S. package insert (3). There are many anecdotal papers reporting MMC toxic effects in one or two patients in which the role of MMC as a causative agent is not clear. A brief but thorough review of MMC toxicities other than myelosuppression has been reported by Verweij (223). The most important is haemolytic uraemic syndrome (HUS) which, based on a literature review, is thought to be dose-dependent (224) with a total dose of 30 mg/M² considered safe. A toxic interaction of MMC with tamoxifen causing HUS has been noted (225, 226), but the roles of the two other agents in the 3 M combination (mitoxantrone and methotrexate) were not clearly defined. Treatment with erythropoietin (226) and plasmapheresis (227, 228) has been helpful in managing HUS.

There are hints of a dose response for activity in treating several neoplasms with MMC. Given the above reported increased risk of non-haematologic toxicities with higher total dose suggests using MMC for two doses only (e.g. 15 mg/M² twice or 20 mg/M² followed by 10 mg/M²) then continuing treatment with other agents in a combination for consolidation purposes.

DISCUSSION AND CONCLUSIONS

There has been consistent evidence that MMC has single agent activity in a number of neoplastic diseases. In most cases, response rates are low and of short duration; however, the activity can range from marginal (e.g. colon cancer) to substantial (e.g. bladder cancer). The cumulative haematologic toxicity of MMC suggests that use with other myelotoxic drugs must be undertaken with caution. Likewise the non-haematologic toxicities of MMC, which seem to be cumulative, indicate that MMC is not a candidate for high dose/rescue strategies and hazardous for use in the adjuvant setting. In certain combinations, MMC has demonstrated a degree of potentiation and palliative utility. One of the continuing problems with an older drug such as MMC is the constant introduction of new therapies which can immediately alter the role of an older drug and necessitate that its use be redefined. This means, for example, determining whether MMC should be used prior to, together with, or as salvage after a new treatment. In the case of a generic drug such as MMC, there is no incentive for a pharmaceutical company to spend money on the necessary research to define its continuing role in these circumstances. Hopefully, government and foundation resources might consider this need of sufficient merit to engage in both preclinical and clinical research. This scenario is further confounded by the increasing number of new therapeutic strategies being introduced. For example, two therapeutic monoclonal antibodies (rituximab and trastuzumab) are already on the U.S. market (3), a large variety of signal transduction inhibitors are in clinical trial (229) and the recent discovery of high levels of cyclooxygenase-2 (COX-2) expression in several tumour types (230) suggests new interventions in the cancer process using selective COX-2 inhibitors. Favourable interaction of MMC + a COX-2 inhibitor has already been demonstrated preclinically (231). The integration of all these discoveries with old and new cytotoxic treatments will require intensive research efforts.

In conclusion, MMC is highly active and should have a continuing role in the treatment of bladder cancer (local). It has established activity which is useful in breast, head and neck and non-small-cell lung cancer, but will need to be re-defined in the context of new treatments. Mitomycin C historically has been quite active in cervical, gastric and pancreatic cancer, but it is being displaced by other approaches. Mitomycin C has marginal activity in colon cancer and probably is no longer of therapeutic value in the treatment of this disease. Continuing research will be essential in constantly redefining the role of MMC as a cancer chemotherapeutic agent.

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