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CLINICAL APPLICATIONS OF QUINONE-CONTAINING ALKYLATING AGENTS

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1. ABSTRACT

Quinone-containing alkylating agents are a class of chemical agents that have received considerable interest as anticancer drugs. These agents contain a quinone moiety that can be reduced and an alkylating group that can form covalent bonds with a variety of cellular components. The oxidation state of the quinone element can modulate the activity of the alkylating element, and reduction of the quinone is required for activation of the alkylating activity of many of these agents. The quinone element may also contribute to the cytotoxic activity of quinone-containing alkylating agents through the formation of reactive oxygen species during redox cycling. The natural product, mitomycin C, has been the most widely used quinone-containing alkylating agent in the clinic, but other quinone-containing alkylating agents like porfiromycin, diaziquone, carbazilquinone, triaziquone and EO9 havealso been used in the clinic for the treatment of cancer. In addition, many other quinone-containing alkylating agents have been tested

in preclinical studies and the development of new agents is being actively pursued. This chapter describes the current and past clinical uses of these agents in the treatment of cancer and discusses new agents that are currently in clinical trials.

2. INTRODUCTION

2.1. Historical Perspective

Quinone-containing alkylating agents are a class of chemical agents that have received considerable interest as anticancer drugs since the late 1950s (1). These agents contain a quinone moiety that can be reduced and an alkylating group that can form covalent bonds with a variety of cellular components. Simple alkylating agents were among the first effective agents for the treatment of cancer (2). The nitrogen mustard, HN2, was first tested in the clinic in 1942, and this agent is still used clinically for the treatment of lymphomas (3). Other nitrogen mustards like chlorambucil, melphalan and cyclophosphamide were introduced shortly afterwards and remain important drugs in many treatment regimens (4). Other alkylating agents ontaining methane sulfonates, like busulfan (5), and aziridines, like thiotepa (6) were also early antitumor agents. Putter (7) suggested that combining a benzoquinone with alkylating groups would produce compounds with potent antitumor activity. This suggestion was supported by the studies of Holzer et al (1) who showed that a number of aziridinyl benzoquinones had very good antitumor activity, and by the isolation of the quinone-containing mitomycin antitumor antibiotics (8,9). Mitomycin C was extensively tested in animals (8,10) and humans (11-13) in the late 1950s and early 1960s, and was shown to be an effective clinical agent. These findings prompted a proliferation of synthetic and biological studies of quinone-containing alkylators as potential antitumor agents (14-16). Many of these agents showed good antitumor activity in cell culture or animal models.

Studies of the mechanism of action of mitomycin C demonstrated that this agent required reductive activation, which was followed by the formation of DNA adducts and strand breaks (17,18). This finding was consistent with earlier predictions by Ross (19) that the oxidation state of the quinone group could influence the activity of an adjacent alkylating moiety. Sartorelli et al. (20) used this principle to prepare a series of benzoquinone and naphthoquinone compounds, which had the potential to alkylate after reduction, as potential “bioreductive alkylating agents”. These agents were able to bind to DNA and demonstrated antitumor activity (20). These studies lead to increased interest in the development of quinone-containing alkylating agents as antitumor agents and in understanding their mechanism of action.

2.2. Mechanism of Action of Quinone-containing Alkylating Agents

Quinone-containing alkylating agents contain two important structural elements that contribute to their activity. The alkylating element can form covalent bonds to cellular components including proteins, membranes and DNA; however, the interaction with DNA is generally thought to be the most important contributor to the antitumor activity of these agents (21). This interaction can result in the formation of DNA monoadducts, or in the case of bifunctional alkylating agents, DNA crosslinks (22,23), leading to the induction of apoptosis (24) and cell death (25). The oxidation state of the quinone element can modulate the activity of the alkylating element, and reduction of the quinone is required for activation of the alkylating activity of agents such as mitomycin C (26,27) and EO9 (26,28). The most important activating enzymes for quinone-containing alkylating agents appear to be the one-electron reducing enzyme, NADPH:cytochrome P450 reductase (21,27,29,30), and the two-electron reducing enzyme, NAD(P)H:quinone oxidoreductase (DT-diaphorase) (21,29,31-34). However, not all agents may require reductive activation (35), and reduction of the quinone group by some enzymes may decrease the activity of these agents (36). The quinone element may also contribute to the cytotoxic activity of quinone-containing alkylating agents through the formation of reactive oxygen species during redox cycling. Reactive oxygen species can damage cellular components, including DNA (21,23,37,38), but this seems to be a minor contributor to the antitumor activity of bioreductive agents (39,40).

2.3. Clinical Application of Quinone-containing Alkylating Agents

The natural product, mitomycin C, has been the most widely used quinone-containing alkylating agent in the clinic, but other quinone-containing alkylating agents like porfiromycin, diaziquone, carbazilquinone, triaziquone and EO9 have also been used in the clinic for the treatment of cancer. In addition, many other quinone-containing alkylating agents have been tested in preclinical studies and the development of new agents is being actively pursued. This chapter will describe the current and past clinical uses of these agents in the treatment of cancer and will discuss new agents that are currently in clinical trials.

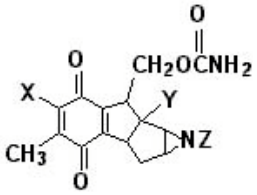
3. CLINICAL APPLICATIONS OF MITOMYCINS

3.1. History

The mitomycins were first discovered by Hata et al (8) in 1956, and mitomycin C was isolated by Wakaki et al (9) from *Streptomyces caespitosus* in 1958. Four mitomycins occur naturally (Figure 1). All are antibiotics effective against both gram positive and gram negative bacteria (41), but only mitomycin C and porfiromycin have appreciable anticancer activity. Mitomycin C has been used clinically in Japan since the early 1960's (42), but this agent was not approved for general use in North America until 1974 (43). Since then mitomycin C has been used to treat a wide variety of solid tumors, but its utility has been decreased by toxicity. Porfiromycin has also received limited clinical use, and a number of mitomycin analogues have been investigated (42).

3.2. Mechanism of Action

The mitomycins require intracellular activation (26) by one electron reducing enzymes like NADPH:cytochrome P450 reductase (26,39) or NADH:cytochrome b_5 reductase (44), or by two electron reducing enzymes like DT-diaphorase



	X	Y	Z
Mitomycin A	OCH_3	OCH_3	H
Mitomycin B	OCH_3	OH	CH_3
Mitomycin C	NH_2	OCH_3	H
Porfiromycin	NH_2	OCH_3	CH_3
BMY-25282	$N=CHN(CH_3)_2$	OCH_3	H
BMS-181174	$NH(CH_2)_2SS\text{-}C_6H_4\text{-}NO_2$	OCH_3	H
KW2149	$NH(CH_2)_2SS(CH_2)_2NHCO(CH_2)_2CH(NH_2)CO_2H$	OCH_3	H
M83	$NH\text{-}C_6H_4\text{-}OH$	OCH_3	H

Figure 1. Structures of mitomycins

(21,31) or xanthine dehydrogenase (45); however, NADPH:cytochrome P450 reductase (21,29,30) and DT-diaphorase (28,29,31-34) are the most important activating enzymes. Reduction of the mitomycins activates the aziridine and carbamate alkylating groups and results in the formation of DNA crosslinks which appear to be the primary mechanism for the antitumor effects of these agents (21-23). If oxygen is present, the reduced mitomycin products can redox cycle to form reactive oxygen species. Reactive oxygen species damage cellular components, including DNA (21,23,37,46), but this seems to be a minor contributor to the antitumor activity of these agents (39). The mitomycins are generally more active under hypoxic conditions and can act as radiosensitizers (26,33).

3.3. Mitomycin C

3.3.1. Clinical Applications

Mitomycin C has been used for the clinical treatment of human cancers for more than 25 years. Despite multiple clinical trials, the use and effectiveness of this agent remains confined to a small number of cancer types. Mitomycin C has proved to be most effective in the front line treatment of a small number of solid tumors, such as superficial bladder cancer (47) and gastric (48), pancreatic (49), anal (50) and esophageal (51) carcinomas. It is also used in palliative treatment of advanced cancers or cancers that have become resistant to other forms of therapy, generally in combination regimens with doxorubicin and 5-fluorouracil or with bleomycin and vincristine (43,52,53). However, the activity of this agent in solid tumors and its enhanced effectiveness against hypoxic cells that are resistant to radiation (26) have resulted in continued interest in mitomycin C and the investigation of new approaches to increasing its effectiveness.

Superficial bladder cancer represents approximately 70% of all bladder cancers at time of presentation (47,54). Transurethral resection is the primary treatment for this disease, but tumors will recur in 50% of all patients (54). Thus, patients at highest risk for tumor recurrence generally receive adjuvant intravesical therapy with anticancer drugs such as mitomycin C, thiotepa or doxorubicin, or with immunotherapy with Bacillus Calmette-Guerin (BCG). Many clinical studies have established the effectiveness of mitomycin C for the treatment of superficial bladder cancer, with complete response rates of from 39% to 77% reported (47). The efficacy of mitomycin C in the adjuvant setting in preventing the recurrence of tumors has also been confirmed (47,55). Drug doses of 20-40 mg by instillation after transurethral resection and then weekly for 6 to 8 weeks (47,56) with, or without monthly maintenance treatments have been used (56,57). Furthermore, recent studies comparing mitomycin C and BCG showed that there was no difference in tumor progression or survival with these two agents, but that BCG might be superior in preventing tumor recurrence (56) possibly at the expense of greater adverse reactions (58).

Adenocarcinoma of the stomach is a highly malignant tumor with a poor prognosis (49). This disease is a major cause of cancer mortality in Japan and other Asian countries, and many patients present with advanced disease which is not curable by surgery alone (48). Mitomycin C has been used extensively as a single agent in the treatment of gastric cancer, especially in Japan with an overall objective response rate of 30% (49). This compares favorably with other single agent therapy with 5-FU or doxorubicin. More recently, mitomycin C has also been extensively used in a number of combination chemotherapy regimens, most notable in the FAM regimen with 5-FU and doxorubicin (48,49,59,60). Mitomycin C is typically given as an *i.v.* bolus at 10 mg/m^2 on day 1 of a 6 to 10 week cycle. The response rates have been approximately 30% with a small number of complete responders. Although this adjuvant treatment increased the time to progression it did not alter survival time in patients with more advanced disease (49). Thus, mitomycin C regimens provide only limited benefit in gastric cancer.

Pancreatic carcinoma has a similar incidence to gastric cancer in North America and also has a poor prognosis. This disease is highly resistant to chemotherapy

but response rates of approximately 25% have been seen with 5-FU or mitomycin C as single agents or with combinations of these agents (49). However, these treatments have little effect on overall survival. More recent trials to investigate the use of preoperative radiation and chemotherapy with 5-FU and mitomycin C to enhance resectability have provided encouraging results (61,62).

Epidermoid carcinomas of the anal region represent only a small proportion of large bowel cancers (63). When these cancers were treated by radical surgery, the 5-year survival rate ranged from 40% to 60% with local relapses being common. More recently, radiotherapy combined with 5-FU and mitomycin C have been extensively used in the treatment of this disease. A number of clinical trials have demonstrated that the concomitant use of radiotherapy and chemotherapy produced a significant improvement in locoregional control and a reduction in the need for surgery (64) and that mitomycin C increased colostomy-free and disease-free survival (63). This regimen has become the standard of care in many centers. Mitomycin C is usually given as an *i.v.* bolus at from 10 to 15 mg/m^2 on day 1 of treatment, with a second dose given at 6 weeks in some cases.

Although carcinoma of the esophagus is still a relatively uncommon disease in North American, the incidence of this disease is increasing and overall 5-year survival rates are only 20%. While this disease is primarily treated by surgery many studies have demonstrated the utility of preoperative concurrent chemoradiotherapy (65,66). Such treatment produces complete response rates of approximately 25% for both squamous cell carcinoma and adenocarcinoma, and may provide a slight survival advantage (66). The chemotherapy regimens normally contain 5-FU with mitomycin C or cisplatin (51,65,66). While combinations with mitomycin C or cisplatin produced similar results (66), the latter agent is more commonly used.

Numerous studies have shown that mitomycin C, used as a single agent, can produce good response rates in a wide variety of solid tumors (43). Thus, this agent is used in the palliative treatment of a number of advanced cancers. In patients with advanced non-small cell lung cancer, combinations of mitomycin C with cisplatin and vinca alkaloids (67) or cyclophosphamide (68) produced high response rates and a moderate increase in survival time. Similarly, the MMM combination of mitomycin C, mitoxantrone and methotrexate produced good response rates in advanced breast cancer (69), which were comparable to other regimens (70,71). However, these regimens have received only limited use because of their high toxicity.

3.3.2. Clinical Studies

Although the current clinical use of mitomycin C is limited, this agent continues to be a focus of many clinical trials because of its intrinsic activity in many solid tumors and its preferential activity in hypoxic cells (26). A number of clinical trials have used this agent as an adjunct to radiotherapy, particularly in tumors that are routinely treated by radiotherapy. These trials are based on the premise that mitomycin C may produce a synergistic effect with radiation by acting as a radiosensitizer and by targeting hypoxic cells in the tumor which are resistant to radiation (26,72). For example, two studies using mitomycin C as an adjunct to radiation therapy in patients with squamous cell carcinoma of the head and neck demonstrated a significant improvement in the local regional relapse and recurrence-free survival for patients receiving mitomycin C treatment (73,74). In addition, a study of concomitant radiotherapy with mitomycin C and bleomycin in inoperable head and neck cancer showed that the chemotherapy significantly increased the complete remission rate and disease-free survival in all the patients studied (75). The combination treatment had an even greater effect on the complete remission rate and disease free-survival in patients with oropharyngeal carcinoma and also increased the overall survival in this sub-group of patients from 10% to 38% (75).

Similarly, radiotherapy is standard treatment for women with locally advanced cervical cancer, but this treatment fails to control disease progression within the irradiated field in 40% of women (76). Thus, there has been interest in combining radiation with chemotherapeutic agents that are radiosensitizers or that target hypoxic cells. A number of studies have examined both concomitant and neoadjuvant chemotherapy with radiotherapy in the management of locally advanced (76,77) and advanced (78) cervical carcinoma, using drug combinations of mitomycin C with 5-FU and/or cisplatin. A number of studies have also demonstrated excellent response rates and improved survival using combination therapy with radiation and mitomycin C, cisplatin and vinca alkaloids in stage III non-small-cell lung cancer (79,80).

Alternatively, mitomycin C containing chemotherapy regimens have been studied for induction therapy prior to surgery in a number of different types of cancer. For example, various combinations of mitomycin C, 5-FU, vincristine and bleomycin have been used to shrink locally advanced cervical cancer prior to radical hysterectomy (81,82). Preoperative chemotherapy with mitomycin C, vinca alkaloids and cisplatin in advanced non-small-cell lung cancer produced high response rates, high complete resection rates after response to chemotherapy and increased survival rates (83-85). A recent study also demonstrated the feasibility of preoperative chemotherapy with mitomycin C, vinblastine and cisplatin in early stage resectable non-small-cell lung cancer and a phase III trial has now been initiated (86).

Combination chemotherapy regimens containing mitomycin C have also been extensively studied for treatment of a variety of resistant and recurrent cancers. In a small trial, mitomycin C with 5-FU and folinic acid produced a rapid improvement in performance status and a reduction of analgesics in approximately 80% of patients with advanced breast cancer that had failed first- and second-line chemotherapy (87). Mitomycin C with methotrexate, vincristine and a steroid produced a 30% response rate in women with advanced breast cancer who

were resistant to doxorubicin or who had relapsed after doxorubicin treatment (88). Mitomycin C with cisplatin and/or doxorubicin also produced approximately 20% response rates in malignant mesothelioma, a disease which has a very poor prognosis (89,90). A 21% response rate was seen with bleomycin, mitomycin C and cisplatin in advanced squamous carcinoma of the uterine cervix (91) and mitomycin C, ifosfamide and cisplatin produced a 56% response rate in inoperable non-small cell lung cancer (92).

3.3.3. Toxicity

Although mitomycin C is an active anticancer drug, its use in the clinic has been severely restricted by its toxicity. Usual dose-limiting toxicity is myelosuppression, which occurs three to four weeks after drug administration, with recovery within eight weeks (43). This toxicity is dose related, increasing with doses >10 to 20 mg/m^2, but effects are cumulative and can be unpredictable. Generally, thrombocytopenia or leukopenia are most severe, but anemia is also common. The appearance of thrombocytopenia after mitomycin C treatment is frequently delayed. Other common toxicities include anorexia, nausea, vomiting and diarrhea (43).

There are a number of other less common, but potentially serious or fatal, toxicities associated with the use of mitomycin C. Approximately 5% of patients receiving mitomycin C develop severe pulmonary toxicity including noncardiogenic pulmonary edema, interstitial pneumonitis and pleural effusions (93) leading to progressive respiratory insufficiency and death (43). Corticosteroid therapy results in improvement in the pulmonary symptoms in less severe cases (43) and a temporary improvement in severe cases (93). This toxicity does not appear to be dose-related, but the risk may increase with exposure to high oxygen concentrations or when mitomycin C is combined with other anticancer drugs like bleomycin which can also cause pulmonary toxicity (43). Between 4% and 15% of patients treated with mitomycin C develop a syndrome known by a number of different names including cancer-associated hemolytic-uremic syndrome (C-HUS) (43,94). This syndrome comprises a complex of microangiopathic hemo;ytic anemia, thrombocytopenia and renal failure that may lead to death. The syndrome is most common in patients that receive six to twelve months of mitomycin therapy or total doses >60mg (43,94). In addition, mitomycin C extravasation during administration can cause painful skin ulcerations and some cases of severe congestive heart failure have been reported after mitomycin C treatment in patients previously treated with doxorubicin (43).

3.3.4. Dosage and Drug Delivery

Mitomycin C is normally administered *i.v.* at a single dose of 20 mg/m^2 or at 2 mg/m^2/day over 12 days; however, other forms of drug delivery are used or have been studied for specific tumors (43,95). Treatment is repeated every 6 to 8 weeks provided the leucocyte and platelet counts have recovered sufficiently. This dose may be reduced if mitomycin C is combined with other myelosuppressive agents. The median terminal half-lives of the drug in single-agent and combination chemotherapy is approximately 50 and 42 minutes, respectively (43,96). Metabolism of mitomycin C is greatest in the liver, spleen and kidney (43) with hepatic metabolism being the most important route of elimination (43,96). In addition, intravesical administration of mitomycin C at doses of 20 to 40 mg is routinely used for the treatment of superficial bladder cancer (47,56).

A number of other methods for more direct delivery of mitomycin C to tumors have been investigated in order to reduce the systemic toxicity of this agent. For example, hepatic intraarterial infusion has been used for liver metastases from breast cancer (97) or gastrointestinal cancers (98).

A variation of this approach has involved hepatic intraarterial administration of mitomycin C and other chemotherapeutic agents combined with cutting off the blood supply to hepatic tumors by embolization (99). A variety of methods have been used to accomplish the vascular occlusion including the use of lipid particles or collagen. This procedure may prolong the transit time of the drugs through the tumor and may also produce ischemic damage. Alternatively, adjuvant intraportal administration of mitomycin C and 5-FU during surgery and during the early postoperative period appeared to reduced the incidence of liver metastasis and increased survival in patients with colorectal cancer (100). Other approaches have included bronchial artery infusion of mitomycin C in patients with non-small cell lung cancer (101) and direct intratumoral injection of mitomycin C adsorbed to activated carbon particles into pancreatic tumors (102). In addition, the combined use of mitomycin C and hyperthermia has also been investigated (103).

3.4. Porfiromycin

3.4.1. Preclinical Studies

Porfiromycin was first isolated from *Streptomyces ardus* in 1960 (104) and has been shown to have activity against many experimental tumors (105-107). A number of significant differences have been observed between the activity of this agent and mitomycin C. Porfiromycin is less toxic to tumor cells than mitomycin C under aerobic conditions (105-107), but shows similar (105) or greater activity (106) under hypoxic conditions. Thus, porfiromycin has a greater hypoxic:oxic ratio and has greater preferential toxicity to hypoxic cells than mitomycin C. This is likely due to poorer activation of porfiromycin by DT-diaphorase and a greater dependence of this agent on activation by NADPH:cytochrome P450 reductase compared with mitomycin C (108). Other observed differences include a greater specificity for targeting hypoxic regions of tumors (109) and differences in the spectra of toxic lesions produced by porfiromycin and mitomycin C under aerobic and hypoxic conditions (110).

Based on the greater hypoxic:oxic ratio of porfiromycin compared with mitomycin C, porfiromycin was studied as an adjuvant to radiotherapy. Treatment of EMT6 murine breast tumors *in vivo* with porfiromycin and radiation produced synergistic tumor cell kill but only additive cytotoxicity to marrow CFU-GM (72). In another study, it was shown that EMT6 tumors implanted into old mice had a higher proportion of radioresistant hypoxic cells than tumors implanted in young mice; however, combining

porfiromycin with X-rays overcame the radioresistance of EMT6 tumors in the older mice (111).

3.4.2. Clinical Studies

Phase I clinical trials investigated the administration of porfiromycin using multiple doses (112,113) or large intermittent doses (112,114). The major toxicity observed was hematological toxicity, mainly leukopenia and thrombocytopenia (112-114), similar to that observed with mitomycin C (43). These trials also produced objective responses in patients with carcinoma of the cervix, ovary, stomach, head and neck, and colon (114). A number of phase II clinical trials with porfiromycin demonstrated that this agent was useful in disseminated squamous cell carcinoma of the cervix and also showed activity in carcinomas of the lung and head and neck (115). A study comparing the effectiveness of porfiromycin and mitomycin C found that these agents produced comparable results in patients with colorectal carcinoma, gastrointestinal cancer and ovarian cancer (116).

Based on the laboratory studies combining porfiromycin with radiation, porfiromycin in combination with radiation therapy for squamous cell carcinoma of the head and neck was studied in a phase I clinical trial (117). Patients with locally advanced disease and a low probability of cure were treated with standard fractionated daily radiation, and porfiromycin was administered on days 5 and 47 of the course of radiation therapy. This treatment regimen resulted in acceptable acute hematological and nonhematological toxicities, and produced a 5 year disease free survival rate of 32%. Based on these results a phase III trial comparing porforomycin and radiation therapy with radiation therapy alone in squamous cell carcinoma of the head and neck has been initiated.

3.5. Other Mitomycin Analogues

3.5.1. Preclinical Studies

While both mitomycin C and porfiromycin have very good antitumor activity in a variety of solid tumors, their clinical use has been limited by cumulative myelosuppression and C-HUS. Thus, there has been considerable interest in developing mitomycin analogues with decreased toxicity and increased antitumor activity. Most studies have focussed on substitutions at the C7 amino group of mitomycin C or porfiromycin (118). Although many mitomycin analogues have been prepared and have been tested for antitumor activity, only a small number of these compounds have been targeted for further development.

The 7-*N*-(dimethylamino methylene) analogue of mitomycin C, BMY-25282, was more potent in a number of different mouse tumors *in vitro* and *in vivo*, showed greater activity under aerobic conditions and generated more oxygen radicals than the parent compound (119,120). This agent had a lower quinone-containing reduction potential than mitomycin C (121), and was active in human colon carcinoma cells that were resistant to the parent drug because of deficient activation of mitomycin C (122). However, BMY-25282 showed greater toxicity to neonatal rat-heart myocytes than mitomycin C (123) and produced delayed cardiac toxicity in rats *in vivo* (124). Thus, this agent was not tested in humans.

M83, a 7-*N*-(4-hydroxyphenyl) analogue of mitomycin C, showed greater potency than the parent drug against a number of rodent leukemia, lymphoma and solid tumors *in vivo* (125). This agent also produced lower myelosuppression and leukopenia than mitomycin C and had a markedly increased therapeutic index in these rodent models (125). In contrast, M83 showed similar activitity to mitomycin C in human tumor xenografts (126). However, based on the lower toxicity in the rodent model, M83 was tested in a phase I-II clinical study (127).

The 7-*N*-(2-(4-nitrophenyldithio)ethyl) analogue of mitomycin C, BMS-181174 (formerly known as BMY-25067), was shown to have superior activity against solid tumors in mice compared to mitomycin C (128). In addition, this agent was less neutropenic and thrombocytopenic than mitomycin C (128), and produced only minor renal changes with no cardiac or pulmonary toxicity in animals (124). BMS-181174 was more potent under aerobic conditions than under hypoxia and may produce its cytotoxic effects by a different mechanism than the parent compound (129,130). Based on these considerations BMS-181174 was evaluated in a phase I trial (131).

KW2149, 7-*N*-(2-((2-(gamma-L-glutamylamino) ethyl)dithio)ethyl)mitomycin C (also known as KT6149) is a water soluble mitomycin analogue (132) that showed enhanced antitumor activity against human tumors *in vitro* (133) and in nude mice (134). The mechanism of antitumor activity of this analogue may be similar to that of BMS-181174 (130). KW2149 has not yet been tested in the clinic.

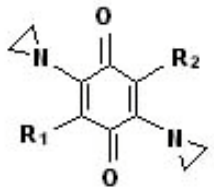
3.5.2. Clinical Studies

To date only M83 and BMS-181174 have been studied in the clinic. A phase I-II study of M83 in 22 patients found that this analogue produced hematological and non-hematological toxicities that were very similar to those seen with mitomycin C and only one objective response was observed (127). Based on this initial study it was suggested that this agent was not superior to the parent drug and no further clinical studies were carried out. A phase I trial with BMS-181174 found that myelosuppression, particularly thrombocytopenia, was the dose limiting toxicity (131). Other toxicities included thrombophlebitis, pneumonitis and possible cardiotoxicity and renal damage. Although this agent showed antitumor activity in previously treated and untreated patients, no further clinical studies are planned.

4. CLINICAL APPLICATIONS OF BENZOQUINONE-CONTAINING ALKYLATING AGENTS

4.1. History

Benzoquinone-containing alkylating agents were amongst the first quinone-containing alkylating



	R_1	R_2
Diaziquone (AZQ)	$NHCO_2CH_2CH_3$	$NHCO_2CH_2CH_3$
Carbazilquinone	CH_3	$CH(OCH_3)CH_2OCONH_2$
Triaziquone	N◁	H
BZQ	$NHCH_2CH_2OH$	$NHCH_2CH_2OH$
RH1	CH_3	CH_2OH

Figure 2. Structures of benzoquinone-containing alkylating agents

agents studied as possible anticancer drugs. Putter (7) suggested that adding alkylating groups to the benzoquinone structure would produce compounds with potent antitumor activity

Holzer et al (1) provided support for this suggestion by demonstrating that a number of aziridinyl benzoquinones had very good antitumor activity. This lead to the synthesis and testing of a large number of benzoquinone analogues having differing alkylating groups (14-16). The majority of these analogues had either an aziridine (1,14-16) or nitrogen mustard (14) alkylating group; however, a variety of other alkylating groups were also investigated (14,15,20). While some of these agents showed good activity in tumor cells or animal models many of them also produced major toxicities, particularly hematological toxicity (14). To date only four benzoquinone-containing alkylating agents, diaziquone (AZQ), carbazilquinone, triaziquone and BZQ, have been used in the clinic, although other agents such as RH1 (135) have received considerable attention recently (Figure 2).

4.2. Diaziquone

4.2.1. Preclinical Studies

Diaziquone was first tested as a potential central nervous system antitumor agent in the early 1960's and was shown to have significant activity in both intracerebral and intraperitoneal mouse leukemia models, as well as activity in solid tumors (136,137). The mechanism of action of diaziquone is still not fully understood but appears to result from DNA alkylation, crosslinking and strand break formation (138). Studies by Gutierrez et al (139) have shown that this agent is reduced by NADPH:cytochrome P450 reductase to the semiquinone species which generates reactive oxygen species by redox cycling in the presence of oxygen. However, diaziquone has also been shown to be a substrate for DT-diaphorase (140,141), and reduction of the quinone by this enzyme resulted in increased DNA crosslinking, oxygen radical formation and cytotoxicity (140-142). It is still not clear which of the two activation pathways and which types of DNA damage are most important for the antitumor activity of this agent (140,141).

4.2.2. Clinical Studies

Phase I studies investigated the use of diaziquone by daily (143) or weekly (144) *i.v.* injection, by monthly intraarterial infusion (145) or by twice-weekly or weekly intrathecal injection (146). The dose limiting toxicities were generally leukopenia and thrombocytopenia (143-145), while gastrointestinal toxicity (144,145) and headache (146) were also common. Diaziquone was rapidly removed from plasma by a two-compartment open-system model (143,144), and the agent was found at appreciable levels in the cerebrospinal fluid (146,147). A number of complete and partial responses were seen in patients with meningeal leukemia (146) and malignant astrocytomas (145).

Based on preclinical studies and phase I clinical trials, diaziquone has been studied in the treatment of CNS tumors. A number of clinical trials showed response rates of approximately 20% in patients with high-grade or progressive gliomas treated with diaziquone (148,149) and approximately 25% in patients with astrocytic neoplasms treated with diaziquone and either BCNU or procarbazine (150). However, phase III trials comparing diaziquone to the nitrosoureas, BCNU or PCNU, found that diaziquone was not significantly better than BCNU (151) and was less effective than PCNU (152) in patients with brain tumors.

The activity of diaziquone in a wide variety of leukemias, lymphomas and solid tumors has been extensively studied. This agent produced responses in 30% of patients with relapsed acute nonlymphocytic leukemia (153,154) and in 20% of patients with refractory lymphoma (155,156) or acute myeloid leukemia (157). In contrast, the drug was not active in patients with resistant multiple myeloma (158,159). Diaziquone produced only minor responses in patients with head and neck (160), ovarian (161), lung (162,163), colorectal (164,165), breast (166), cervical (167), uterine (168), gastric (169), pancreatic (170) and renal (171) cancer, and was inactive in soft tissue and bony sarcomas (172) and melanomas (173). Diaziquone has also been extensively evaluated in pediatric tumors. It produced a 10% response rate in recurrent pediatric brain tumors (174,175), but had little effect in other solid tumors (174) or acute leukemias (176). In addition, because diaziquone shows little non-hematopoietic toxicity, it has been investigated for inclusion into bone marrow transplant preparative regimens (177).

Despite showing good activity in recurrent or resistant brain tumors, nonlymphocytic leukemias and

lymphomas, diaziquone is not currently in general use. This is likely due to its toxicity and because it did not demonstrate clearly superior effectiveness to existing or newer chemotherapeutic agents.

4.3 Carbazilquinone

4.3.1 Preclinical Studies

Carbazilquinone was first synthesized in 1970 as a mitomycin C analogue having a quinone group and aziridine and carbamate alkylating groups (178). This agent showed good activity in mouse tumors *in vivo* including plasmacytoma, lymphoid leukemia and Ehrlich carcinoma, and was more effective than mitomycin C in the latter two tumors (179). It also showed good antitumor activity in human primary tumor specimens of urothelial transitional-cell carcinoma (180), lung cancer (181), hepatocellular carcinoma (182), squamous cell carcinoma (183) and gastric cancer (184) *in vitro*, and in human ovarian (185) and pancreatic (186) tumor xenografts in nude mice. The mechanism of action of carbazilquinone is not completely understood, but it is thought that this agent acts as an alkylating agent (187). The drug is a substrate for both NADH (188) and NADPH-dependent (189) reductive enzymes; generates reactive oxygen species (189); produces DNA strand breaks (190), and is more active under hypoxic conditions (191). Thus, carbazilquinone is likely a bioreductive agent and production of DNA strand breaks through the generation of reactive oxygen species may also contribute to its antitumor activity.

4.3.2 Clinical Studies

Carbazilquinone has been extensively studied in the clinic, primarily in Japan, since the 1970s. Initial studies suggested that this agent had activity as a single agent in gastric, ovarian and hematological cancers (187). Later studies found response rates of from 6% to 30% in lung tumors (192-194), 60% in gastric tumors (195,196) and 40% in ovarian tumors (197)when the agent was combined with other antitumor agents or immunotherapy. Carbazilquinone also produced a 60% response rate when used with doxorubicin and bleomycin in patients with superficial bladder cancer (198), but lower response rates were seen with doxorubicin, mitomycin C, cisplatin or 5-FU in prostate (199) or liver cancer (200). However, this agent appeared to be highly effective in patients with hematological disorders including chronic myelogenous leukemia, lymphomas, multiple myeloma, polycythemia vera and essential thrombocythemia (201-203).

Initial studies indicated that carbazilquinone produced the usual toxicities associated with mitomycin C analogues. Leukopenia, thrombocytopenia and anorexia were the major toxic effects of the drug, but there was no evidence of toxicity to the liver or kidneys (187). However, more recent studies suggest that this agent may promote transformation of some myeloproliferative disorders to acute leukemias (203). In a controlled study 17% of patients with polycythemia vera and 31% of patients with essential thrombocythemia that were treated with carbazilquinone had transformations to acute leukemia and there appeared to be a relationship between the dose of drug received and transformation (203). Thus, there has been little use of this agent in North America or Europe.

4.4 Other Benzoquinone-containing Alkylating Agents

4.4.1 Preclinical Studies

Triaziquone was first synthesized in 1958 (204) and was shown to have activity in a variety of different animal tumors *in vitro* and *in vivo* and in human tumors including Jensen sarcoma (205), Ehrlich mouse carcinomas and GW77 human colon carcinoms (206) and rat Yoshida sarcoma (207). This agent presumably produces its antitumor effects by alkylation of cellular components (208), and has been shown to inhibit DNA and RNA synthesis (209,210). Triaziquone may block synthesis of deoxynucleotide bases (209) and interacts with the plasma membrane (211). More recent studies suggest that this agent is a substrate for both one and two-electron reducing agents and that the cytotoxic activity may result from protein alkylation and oxidative stress (212,213).

BZQ was first synthesized in 1976 (137) and showed good activity against intraperitoneal mouse leukemias and melanoma (214). This agent had only moderate activity in an intracerebral mouse model (214), but showed good activity in human colon carcinoma (215) and human leukemia cells (216) *in vitro*. Mechanistic studies suggested that BZQ was not a substrate for DT-diaphorase (215) and did not produce DNA strand breaks (217). However, it produced DNA crosslinking without reduction and this was enhanced under acidic conditions (218). Thus, the cytotoxicity of this agent appeared to be due to its alkylating activity, and the drug probably does not act as a bioreductive agent (219).

4.4.2 Clinical Studies and Use

Triaziquone was used clinically in the 1960s for the treatment of a number of cancers (220). It was used intravenously in the treatment of leukemias and lymphomas like chronic lymphocytic leukemia and Hodgkin's disease, and for ovarian cancer. The agent was also used as an ointment for basal cell skin cancers. Because of its toxicity to bone marrow and blood vessel walls it has been replaced by more effective agents and has not been used clinically for many years. A more recent study of this agent as an adjuvant to surgery in carcinoma of the cervix found that there was no difference in 5 year survival between the triaziquone treated patients and patients receiving conventional therapy (221).

BZQ has received only minimal investigation in humans. A pharmacokinetic study showed that, like diaziquone, this agent was rapidly removed from the plasma but had much lower plasma protein binding than diaziquone (222).

5. CLINICAL APPLICATIONS OF INDOLOQUINONE-CONTAINING ALKYLATING AGENTS

5.1. History

Following the isolation of mitomycin C and its identification as a potent antibiotic and antitumor agent,

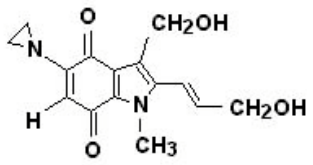


Figure 3. Structure of EO9

there was considerable interest in developing simpler synthetic analogues. Because the mitomycin structure contains the indoloquinone ring system, indoloquinone analogues were synthesized and tested for their biological activity (223). While many of these compounds demonstrated antibiotic activity, most did not show good antitumor activity (223). There was renewed interest in the indoloquinones as antitumor agents in the 1980s with new analogues being prepared (224,225) and tested for biological activity. This interest has continued to the present time with many structure-activity studies aimed at identifying new bioreductive agents being reported (226-229). However, to date only one indoloquinone, EO9, has been tested in the clinic (Figure 3).

5.2. EO9

5.2.1. Preclinical Studies

EO9 was synthesized in 1987 (225) and its antitumor activity has been extensively studied in animal and human tumors (230). EO9 showed very good antitumor activity in many human tumor cell lines *in vitro* and displayed preferential activity in cell lines derived from solid tumors in the NCI human tumor screen, particularly colon, melanoma, central nervous system, renal and non-small cell lung tumors (230,231). This agent was also very potent in a number of *in vivo* murine tumors and human tumor xenografts, but showed little activity in leukemias (231). In addition, EO9 produced no significant bone marrow toxicity in mice. However, preclinical studies in animals found that the drug was rapidly eliminated (232).

The mechanism of action of EO9 has also been extensively studied. The agent is reduced by both one and two-electron reducing enzymes (233-235) and produces DNA strand breaks (234) and crosslinks (233,235) following reduction. The two-electron reducing enzyme, DT-diaphorase, appears to be the most important activating enzyme for EO9 under aerobic conditions, and the sensitivity of cells to this agent correlated with the level of the enzyme under these conditions (236,237). EO9 showed enhanced activity under hypoxic conditions; however, DT-diaphorase appeared to decrease the activity of the agent under these conditions (238).

5.2.2. Clinical Studies

Based on the selective activity of EO9 toward solid tumors, its preferential toxicity to hypoxic cells and its low marrow toxicity, this agent was entered into clinical trials. Two phase I studies found that the drug was rapidly eliminated from the plasma following intravenous injection, but did not produce any bone marrow suppression (239, 240). The dose-limiting toxicity was proteinurea (239). Phase II clinical trials with EO9 confirmed the renal toxicity and lack of myelosuppression with the drug; however, the agent showed no antitumor activity in breast, gastric, pancreatic, colorectal or non-small cell lung cancer (241, 242). This failure has primarily been attributed to the rapid clearance of the agent from the body.

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