Cancer Chemother. Pharmacol. 1, 15–24 (1978)

Cancer Chemotherapy and Pharmacology

Short Review

New Drugs under Clinical Evaluation in the United States

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Drugs in clinical trial in the United States came from a variety of sources. Most are sponsored for clinical trial by the National Cancer Institute and some by the pharmaceutical industry. Compounds originally developed and tested abroad constitute a significant fraction highlighting the importance of international cooperation in cancer chemotherapy. There are a wide range of ways to separate out the drugs currently under clinical investigation. One approach is new structures versus analogues. Another approach is drugs originating from outside the U.S. as against those from within. In this paper an attempt will be made to briefly review the data on a number drugs still investigational in the United States drawn from a mix of new structures domestic and foreign and analogues with the same separation.

Cis-diammine dichloroplatinum (II) (DDP) has been in trial since 1972. It was originally discovered by Rosenberg et al. in 1965 [76]. While investigating the possible effects of an electrical field on bacterial growth processes they noted that the electrical current delivered between platinum electrodes in nutrient broth inhibited the replication of E. coli.

Structurally DDP is an inorganic complex formed by chlorine and ammonia atoms in the cis position in the horizontal plane [39]. The mechanism of action has not been fully elucidated. Derewinko and Gottlieb showed that it had no cell cycle phase specificity in its kill [16]. Similarities between DDP and the bifunctional alkylating [57, 74, 77] agents has been proposed. The drug does crosslink the complementary strands of DNA of HeLa cells [74]. Others have also reported this [57, 62, 63, 83], however there are data indicating that crosslinking is not responsible for most of the observed DNA inactivation [62, 63].

In early clinical trials DDP was administered by rapid intravenous infusion with a variety of dose schedules. The two most commonly used have been 50–75 mg/m^2 once every 3 weeks and 15–20 mg/m^2 daily for 5 days repeated every 3 or 4 weeks. With these schedules a significant degree of cumulative renal toxicity has been reported and for a while it appeared that this would severely limit the clinical usefulness of the drug. Various means have been advocated to alleviate this renal toxicity. These have included slow-drip administration, intravenous hydration [39, 70], and the use of penicillamine [38]. The best results have come with the use of intravenous fluids combined with mannitol and in some cases with diuretic agents [32, 60]. It appears that these latter approaches have solved the renal toxicity problem so that the drug can be widely used.

The other major toxic effects induced by DDP can be classified as gastrointestinal, audiologic, and hematologic. All are dose related, some are cumulative, and it is difficult to concisely summarize their frequency and magnitude. Marked nausea and vomiting occurs in most patients and in some it is so troublesome that it may necessitate withdrawal of the treatment. It usually starts within 1 h after treatment and lasts less than 24 h. Auditory abnormalities are found in approximately 30% of the cases treated on a schedule of 50 mg/m^2 every 3 weeks [51]. They are manifested by tinnitus or hearing loss essentially limited to the high frequency range. The hearing loss can be unilateral [71] and it appears to be cumulative with more likely occurrance on high dose regimens [51, 55]. Its reversibility remains controversial [60, 55, 36].

Transient and moderate myelosuppression may be encountered. This effect appears to be dose related [86] and might be cumulative [55]. At intermittent doses of 50–60 mg/m^2, leukopenia of less than 2,000 cells/mm^3 or thrombocytopenia of less than 50,000 cells/m^3 rarely occurs.

DDP has significant activity against testicular carcinoma. When six studies are totalled the response rate is 66% with 15 complete and 31 partial responses in 70 cases [32, 37, 60, 66, 68]. Most of these patients were previously trated and almost all these responses lasted less than a year. It has been in combination that plati-

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num has found its major role in this tumor type. The best results have been obtained by Einhorn [22]. He has recently reported on 50 patients treated with a three-drug combination of DDP, vinblastine, and bleomycin. This regimen gave a 100% response with 74% being complete. Thirty-eight of these patients remain alive and 32 remain alive and disease-free at 6^+ to 30^+ months.

Golbey at Sloan-Kettering has also integrated DDP into a series of combinations with vinblastine, bleomycin, and actinomycin D [13, 14, 96]. In one of their latest reported regimens cytoxan is also given and in 26 evaluable patients 18 are complete responders.

DDP is also active in ovarian cancer. Wiltshaw [95] has reported responses in eight of 34 patients treated on a variety of schedules. Others have also reported activity [10, 32, 56]. Recently the combination of DDP and adriamycin has been reported as highly active [10].

Hexamethylmelamine (HMM) is one of the substituted melamines derived from cyanuric chloride that was originally investigated for possible use in synthetic resins and fibers [46]. The structural similarity of melamines to the ethylenimonium intermediates in the hydrolysis of nitrogen mustard suggests possible antitumor activity. When triethylenemelamine (TEM) was found to be an active antitumor agent, analog searching led to the discovery of HMM (Fig. 1).

Because of its structural resemblance to TEM, HMM was initially thought to be an alkylating agent. This is unlikely because neither HMM nor any of its metabolites react positively with the nitrobenzyl pyridine (NBP) test, which is an in vitro test for alkylating activity [97]. Further evidence comes from clinical studies where patients have responded to HMM after failure of alkylating agent therapy [82, 85, 93].

There is evidence that some diamino-dihydro-S-triazenes act as folic acid antagonists [3]. Recent data utilizing in vitro assays for inhibition of dihydrofolate reductase from rat liver reveal that neither HMM nor its metabolites inhibit this enzyme [98]. Apparently it is the dihydroxyl group in the triazene compounds which is necessary for the antifol action, and HMM lacks the hydroxyl groups.

It has been reported that HMM (10^{-4} M) inhibits in vitro incorporation of radioactive thymidine ^3H and uridine ^3H into DNA and RNA, thus implicating inhibition of DNA and RNA synthesis as a possible mode of action [33]. In the same experiment, evidence for inhibition of protein synthesis was obtained but a prolonged exposure of cells to HMM (1–3 h) was required to obtain this effect. Although the report suggests that this in vitro effect might parallel the in vivo tumor inhibiting mechanism of HMM, a clear delineation of such antimetabolite activity remains to be explored.

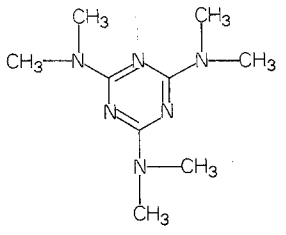

Fig. 1. Structure of hexamethylmelamine

The current heightened interest in HMM stems from the preliminary results of ongoing studies in ovarian cancer where the drug appears to be at least as active as alkylating agents. Furthermore, there is probably no cross resistance between these agents, making it logical to combine them or use one therapy after the patient fails to respond to the other. The results presented here are cumulative of many studies with small numbers of patients and have the inherent problems of retrospective analysis. Although the total number of treated patients in each disease category is small, responses have consistently been observed in carcinoma of the ovary cervix, breast, lung (small cell type), and lymphomas.

Efforts are currently being made to elucidate the exact mechanism of action of HMM. Worzalla et al. [99] are testing the antitumor activity of the various known metabolites of HMM as one potential source of that information. Cross resistance studies involving HMM, alkylating agents, and antimetabolites are under investigation in the Drug Evaluation Branch of the National Cancer Institute (R. Geran: Personal Communication). A new parenteral dose form of HMM is being formulated with a potential for reduced GI toxicity and/or administration of higher total dose of the drug.

Carcinoma of the cervix is another tumor in which HMM produces a respectable response rate of 28% (11/39). The response rates for other single agents active in cervical cancer include: cyclophosphamide 19% (36/197); 5-FU 23% (37/159); bleomycin 10% (8/78); and vincristine 29% (10/34) [38]. HMM thus appears to be an active agent in cervical cancer and should be explored in combination studies.

HMM has definite activity in breast carcinoma that needs to be further explored by combining HMM with other agents in this disease. One combination study using HMM with methotrexate and vincristine has recently been started by Dao and Horton (Personal communication). Further evaluation of HMM should be carried out in cancer of the bladder, uterus, and prostate. Very little data exists concerning the responsiveness of these tumor types to the commonly used anticancer drugs [94]. The hints of HMM activity against these tumors that have been observed in broad Phase II studies should be explored by additional disease specific trials.

In conclusion, HMM has established activity in ovarian and lung cancer, and activity is promising in the lymphomas and carcinoma of the cervix. Its most definitive role is in the treatment of ovarian carcinoma, especially in cases resistant to alkylating agents. HMM combinations with alkylating agents and antimetabolites currently under investigation hold the promise of brightening the future of therapy in this disease.

Anguidine (NSC 141, 537) is the principle phytotoxic metabolic product of the parasitic fungus *Fusarium equiseti.* The drug may be a primary cause in reported cases of toxicosis of humans and animals after ingestion of grain or other products which have been infected with the *Fusarium* species.

Anguidine (diacetoxyscirpenol) is a sesquiterpene isolated from the fungi *Fusarium equiset* [9, 15, 23]. It is closely related structurally to nivalenol, fusarenon-X, and T-2 toxin, compounds which are produced from fungi which damage wheat [67, 87].

Although the chemical properties and stucture of anguidine are well known, the biochemical mechanism of action is not. Recently, Grollman has shown that anguidine inhibits synthesis of protein in HeLa cells and in intract rabbit reticulocytes by 50% at a concentration of 5×10^{-8} M[4]. After incubation of HeLa cells with 10^{-7} M anguidine for 30 min, this effect is irreversible. In rabbit reticulocyte lysates he found that anguidine inhibits globin synthesis by 50% at a concentration of 5×10^{-6} M. DNA synthesis in HeLa cells was partially inhibited by anguidine, but RNA synthesis was not affected. The primary effect of this drug in HeLa cells appears to be on the biosynthesis of protein.

These results are similar to those demonstrated for fusarenon-X by Ohtsubo et al. [67]. The latter compound inhibits protein synthesis. This is associated with a rapid breakdown of polyribosomes. The polyribosome disaggregation does not occur when protein synthesis has been previously inhibited by cycloheximide. Since cycloheximide inhibits chain elongation, the action of fusarenon-X is thought to require an active translation process.

Anguidine, at a concentration of 10^{-3} M, does not inhibit the binding of E. coli ^{3}H-tRNA, ^{3}H-poly U or ^{3}H-poly C to reticulocyte ribosomes, indicating that this earlier stage of protein synthesis is not affected [29]. Further work is needed to determine which step in protein synthesis is inhibited and whether its effect on DNA synthesis is entirely a secondary one.

The basis of selection of anguidine for Phase I trials was activity in the P388 leukemia system which showed a reproducible ILS of 107% on an i.p. daily × 9 schedule with an optimal dose of 1–2.5 mg/kg/inj. When given orally on the same schedule, an ILS of 78% was obtained with an optimal dose of 2.0 mg/kg. Activity was also seen in the L1210 leukemia system where an ILS of 59% was observed when anguidine was given s.c. daily × 13 days at an optimal dose of 1.6 mg/kg/inj. In AKR leukemia, an ILS of 91% was seen when the drug was given i.p. daily × 9 with an optimal dose of 0.2 mg/kg/inj. Marginal activity was seen against i.p. implanted B16 melanocarcinoma, and the drug was negative in the i.m. implanted Lewis lung carcinoma.

Phase I studies have been completed at M.D. Anderson Hospital and at the University of Kansas Medical Center [87]. Patients were treated at doses ranging from 0.2–3.1 mg/m^2 daily × 5. At 2.4 mg/m^2, WBC fell below 3000/mm^3, platelets below 50,000/mm^3, and a drop in blood pressure was also noted. Other toxicities noted at various doses included headache, malaise, and nausea and vomiting which occurred within 1 h after drug administration and lasted up to 4 h. One patient with a liver metastasis exhibited hyperuricemia.

The recommended dose for Phase II clinical trials is 5–7.5 mg/m^2 daily × 5 q 3 weeks by i.v. infusion.

Chlorozotocin is the 2-chloroethyl analog of the nitrosourea, streptozotocin. Biochemical studies have shown that chlorozotocin is relatively cell-cycle specific for a nitrosourea, with much higher killing action for G1 arrest cells than for cells in exponential growth phase.

Chlorozotocin shows good activty against L1210 leukemia, P388 leukemia, and B16 melanocarcinoma, with cures being otained in all three systems. Marginal activity has been seen in subcutaneously (s.c.) implanted Lewis lung carcinoma. The drug is active when given i.p. or s.c. in various schedule dependency tests with L1210, and i.p. regimen of q 3 h on day 1 only gave the most 41 day survivors.

Because of good results in the L1210 system, a later test using a larger innoculum of cells was tried. Tests using 10^7 L1210 cell implants showed best results with a single i.p. dose on day 1.

Chlorozotocin has been compared to streptozotocin, BCNU, CCNU, and MeCCNU with regards to survival and cell cycle progression in both exponentially growing and noncycling G1 arrested CHO cells [89, 90]. The nitrosoureas can be divided into two groups with BCNU and Streptozotocin distinguishable from CCNU, MeCCNU, and Chlorozotocin.

The major properties of CCNU, MeCCNU, and chlorozotocin are as follows: (1) G1 arrested cells are much more sensitive to their killing action than are exponentially growing cells, i.e., they are relatively cell-cycle specific; (2) they do not prevent the initition of DNA synthesis, but do prolong the duration of S-phase. Cells treated with chlorozotocin require twice as long to transverse the S-phase as nontreated cells. (3) They cause the arrest of cells entering G2 phase but are unable to prevent G2 phase cells from progressing through mitosis; (4) chromosomal nondisjunction, polyploidy,

and altered growth morphology are prominent for CCNU and MeCCNU; and (5) chlorozotocin totally blocks transit of cells past an early point in G2. Cells in G1 arrest, G1, and S-phase exposed to chlorozotocin, traversed to G2 phase where cell-cycle progression slowed and subsequently ceased. Only cells already in G2 or M phase during exposure were able to divide, but these cells were ultimately affected by formation of polyploid cells or nondisjunctive errors during the next division cycle.

BCNU differs for CCNU, MeCCNU, chlorozotocin in the following ways: (1) it is relatively less cycle specific, i.e. the difference in sensitivity of G1 arrested and exponentially growing cells to its cytocidal action is much smaller; (2) it slows the transit of G1 cells into S-phase; and (3) it can prevent the progression of all G2 cells through mitosis. Streptozotocin differs from BCNU by being less potent, a 40-fold higher concentration being needed for effect, and because cycling cells are slightly more sensitive to its cytocidal action than noncycling G1 arrested cells. In addition, even at the highest concentrations used, streptozotocin was unable to totally stop progression of cells through G2 phase and mitosis.

Two of the biochemical properties of the nitrosoureas are their ability to alkylate and carbamoylate nucleophilic sites on target molecules. These activities of chlorozotocin were compared to CCNU, MeCCNU, and BCNU [2, 79] (Table 1).

Maytansine is a naturally occurring ansa macrolide and was originally isolated by Kupchan from the East African shrub maytenus ovatus, and later from the wood and bark of *Maytenus budhananii* [54]. The ansa macrolide class includes the ansamycin antibiotics (rifamycins, streptovaricins, tolypomycins, and geldanamycins) known for their inhibitition of bacterial DNA dependent RNA polymerase and viral RNA-dependent DNA polymerase [30, 61, 100]. An ansa structure consists of an aromatic nucleus with a macrocyclic aliphatic bridge attached at two nonadjacent carbons in the ring. Maytansine is the first ansa compound to be isolated from a plant rather than a microorganism. It resembles other ansa compounds in that the chain is joined to the aromatic ring through an amide linkage. Three functional groups, an arylchloride, an epoxide, and a carbonolamine are unique to maytansine. All three groups are possible targets for a nucleophilic attack [72]. Isolation of maytansine from an alcohol extract of plant material was guided by an assay for activity against KB cell culture and in vivo P388 leukemia.

Table 1. Of the group, chlorozotocin has the highest alkylating and lowest carbamyolating activity

NSC	Alkylating activity	Carba-myolating activity	Half-life[a]
79037 – CCNU	100	100	100
95441 – MeCCNU	100	91	100
409962 – BCNU	266	68	81
178248 – Chlorozotocin	452	2	39

[a] Given as a relative percentage

The compound possesses stathmokinetic (mitosis inhibiting) properties inducing metaphase arrest, an action similar to vinca alkaloids such as vincristine. Maytansine is active against P388 leukemia, B16 melanocarcinoma, and Lewis lung carcinoma in vivo. In vitro activity has been demonstrated against KB, L1210, L5178Y, and P388 cells. Both in vivo and in vitro activity is seen at extremely low doses of maytansine. The drug appears to be most active when given i.p. every 3 h on days 1, 5, and 9. P388 leukemia resistant to vincristine has been shown to be cross-resistant to maytansine.

When maytansine was tested in vivo against vincristine-sensitive and resistant cell lines, cross-resistance was observed, but maytansine was active against sensitive strains at a 10-fold lower concentration then vincristine. The drug has been shown to prevent spindle formation and disperse existing spindles in marine eggs. In vitro the drug inhibits the polymerization of the microtubule protein and tubulin by causing a disappearance of 305 rings and rapidly dispersing formed microtubules.

Phase I studies have recently been completed at NCI, the Sydney Farber Cancer Center, M.D. Anderson Hospital, and Mayo Clinic on a variety of schedules. Toxicities observed have included diarrhea, neurologic effects, nausea and vomiting, and myelosuppression. Phase II studies are ongoing.

Neocarzinostatin (NCS) is an antitumor antibiotic produced by streptomyces carzinostatious first isolated by Ishida et al. in Japan [43]. The drug has been clinically studied in Japan since 1973 and has been recently put into trials in the U.S. NCS is an acidic protein macromolecule of molecular weight 10,700, consisting of a single polypeptide chain of 109 amino acids cross-linked by two disulfide bridges.

NCS is highly active against ascitic S-180, leukemia SN-36, Ehrlich's ascitics carcinoma, and L1210 [8, 52, 65]. The drug inhibits specifically the synthesis of DNA in bacterial and mammalian cells and induces DNA degradation in *Sarcinea lutea* without affecting RNA and protein synthesis. Recent studies suggest [78] that in vivo NCS may not penetrate the resting cell. In synchronous DON cells [4] the drug was cytocidal to cells in G1, G2, and M phases. Cells in the S-phase were least affected. Studies on synchronized CHO cells [88] showed that NCS inhibited cells from completing the

G2 phase, preventing mitosis and leading to cell death. Studies in HeLa cells also showed a delay of progressions of cells in G2 with no change in cells in the S-period [53].

Studies in Japan [44, 45, 50, 58, 84] utilized the drug mostly for 4—20 days of daily intravenous injections. Toxicities observed included nausea and vomiting, leukopenia, thrombocytopenia, fever, skin rash, and occasional hypotension and shock. Also seen were hepatic abnormalities and two cases (out of 500) of possible renal damage. Activity was reported in acute adult leukemia, pancreas, and gastric cancer by the Japanese, although the gastrointestinal cancer response rates were not high.

Griffin and Comis [27] have reported on a Phase I study from the Sydney Farber Cancer Center involving 57 patients. The schedule was i.v. daily × 5 in escalating doses from 0.5—2.25 mg/m^2. No reproducible toxicity was seen at doses below 1.5 mg/m^2. Acutely 44% of the patients experienced nausea and vomiting while 65% experienced a rigor on the first day. Myelosuppression was seen with the median day of nadir for thrombocytopenia being day 27. There was no evidence of renal or hepatic toxicity. In evaluable patients responses were rated in $^2/_2$ hepatoma, $^1/_2$ lymphoma, $^1/_3$ pancreas, $^1/_5$ melanoma, and $^1/_7$ lung carcinomas. No responses were seen in eight colon cases.

One of the newer antimetabolities being investigated in the United States is ftorafur (NSC 148958), which was first synthesized in the Soviet Union in 1966. Ftorafur is a pyrimidine antimetabolite structurally similar to 5-FUDR which acts as a weak inhibitor of DNA thymine and RNA pyrimidine synthesis. It is neither a substrate nor an inhibitor of pyrimidine nucleoside phosphorylases [59].

The clinical and experimental antitumor activity of ftorafur is similar to 5-FU, with greatest activity being exhibited in gastrointestinal and breast malignancies, and a suggestion of greater activity than 5-FU in rectal carcinoma. The minimal toxicity of ftorafur, relative to 5-FU, appears to be its greatest advantage and is explained by the slow release of small amounts of 5-FU during metabolism of the chemically unstable ftorafur molecules. Because 5-FU metabolism is slow, ftorafur affords essentially a continuous low dose infusion of 5-FU. The dose of ftorafur in Soviet clinical trials was 30 mg/kg by i.v. infusion every 12 h to a total dose of 30—40 g [6, 47]. The Japaneses, who call the drug Ft-207, used 12—24 mg/kg in divided doses orally with results similar to those obtained by i.v. infusions [31].

The group at Wayne State University [92] has shown that a continuous 120-h infusion of 5-FU produces dose-limiting stomatitis before significant bone marrow suppression. Significant marrow suppression could not be achieved by 5-FU given as a 120-h continuous infusion in 34 patients, inasmuch as severe gastrointestinal toxicity forced the interruption of dose escalation. The antitumor activity was comparable to other approaches. The assumption is that ftorafur given daily × 5 will mimic this schedule pharmacologically.

Ftorafur (1—3 gm/m^2/d × 5 i.v. q 2—4 weeks) has been given to 19 patients with metastatic adenocarcinoma, particularly of the gastrointestinal tract, at M.D. Anderson Hospital [91]. Sixteen patients were evaluable and there were four objective regressions and four patients with stable disease, all with gastrointestinal cancer. Dose-limiting gastroenteric and neurologic toxicities occurred at doses > 2 gm/m^2/d × 5, but myelosuppression was not observed. In 66 courses nausea and vomiting occurred in 56 (85%), chills and fever in ten (15%), ataxia in four (6%), dizziness in two (3%), mucositis in two (3%), and phlebitis in one (2%). The lack of significant myelosuppression at an active dosage level makes the drug attractive for combination use.

Ftorafur has been compared to 5-FU in normal mice and in mice bearing leukemia L1210 [24]. On several schedules of administration, both the toxic and therapeutic doses of ftorafur were uniformly higher than those of 5-FU. While both compounds are active in L1210, the optimal dose produced somewhat higher increases in lifespan than ftorafur. A 5-FU resistant subline of L1210 proved to be totally cross-resistant to ftorafur.

Extensive study of hexitols as anticancer agents has been ongoing in Hungary since 1950 [19, 20, 21]. Compounds which have been given clinical trial from this group include mannitol myeleran, dibromommannitol, and dibromodulcitol. The newest drug to be tried clinically is dianhydrogalactitol (DAG), which is the major conversion reaction product of the treatment of dibromodulcitol by mild alkali or human serum. It is felt that DAG may be the active antitumor component of the substituted hexitols [40, 41, 42].

All the cytotoxic hexitols probably exert their greatest effect through alkylation of DNA [12, 49]. Other postulated mechanisms of action include inhibition of RNA and protein synthesis [34, 35]. DAG has been shown to inhibit DNA, RNA, and protein synthesis to a greater extent than the earlier studied clinical drugs in this class such as dibrodulcitol, and was more effective in cross-linking DNA [69].

DAG has experimental activity in a wide range of systems including L1210, P388 and B-16 melanoma, Ehrlich ascites tumor, Yoshida tumor and S-180 [64]. DAG was the most active agent of 177 tested in the intracerebral mouse ependymoblastoma [25].

Phase I studies in the United States at the University of Kansas Medical Center showed the i.v. MTD to be 30 mg/m^2/d × 5 or 20 mg/m^2/d × 10. Myelosuppres-

sion was dose-limiting with thrombocytopenia being more severe and frequent on the 5-day schedule while both thrombocytopenia and leukopenia were equally prevalent on the 10-day schedule. Of a total of 37 patients, evaluable responses were seen in a single laryngeal carcinoma and lung adenocarcinoma [28].

The Mayo Clinic in a Phase I study treated 50 patients with a dose of 40 mg/m^2/d × 5. The median platelet nadir was 31,000 occurring on day 20 and recovering within 8 days. The WBC nadir was 2300 also by day 20. Anemia, nausea, and vomiting were usually mild to moderate. Responses were reported in two of five patients with hypernephroma who had failed prior therapy with velban and depo-provera [18].

The Eastern Cooperative Oncology Group has done a Phase II study in renal cancer at a dose of 35 mg/m^2/d × 5. This study unfortunately did not reveal any activity. The Mayo Clinic has performed a Phase II study in nonoat cell lung cancer at a dose of 30 mg/m^2/d × 5. Responses were seen in $^4/_7$ squamous lesions, $^1/_3$ large cell, and $^9/_{12}$ adenocarcinomas [17].

Piperazinedione is a crystalline antibiotic obtained from a strain of streptomyces. It was chosen for clinical trial on the basis of activity in the leukemia L1210 system. It appears to be partially cross-resistant with cyclophosphamide and is, therefore, possibly an alkylating agent, although this does not appear to be its only mechanism of action.

A single dose schedule has been tested by M.D. Anderson Hospital [26]. The doses ranged from 1.5–36 mg/m^2 i.v. repeated every 3–4 weeks. Among 45 evaluable patients, including 41 with extensive prior chemotherapy, there were five partial responses and eight improvements (25–50% tumor shrinkage). These included 2 PR in 16 melanomas, 2 PR in two cases of chronic myelogenous leukemia blast crisis, and improvement in six AML patients, one renal carcinoma, and one prostate cancer. Hematologic toxicity was dose-limiting and affected both granulocytes and platelets. Vomiting, anemia, and mild prothrombin time prolongations were the only other toxic effects. Starting doses of 15 mg/m^2 for solid tumors and 24 mg/m^2 for leukemia patients are now being used for Phase II trials.

Roswell Park Memorial Institute [5] chose a weekly schedule for its Phase I study with this drug. Doses were escalated in subsequent patients from 0.3 mg/m^2 week × 5 up to 3 mg/m^2 week × 5, with two patients at each dose level. Fifteen patients were evaluated but no tumor response has been observed. Nausea and vomiting, possibly drug related, was seen in two patients and six patients had transient SGOT elevations. Currently dose schedules of 3 mg/m^2 twice weekly × 3 for hematologic malignancies and 2 mg/m^2 twice weekly × 3 for solid tumors are being explored.

A pediatric Phase I study with piperazinedione has been reported by Pratt et al. [73] at the St. Jude Children's Research Hospital. Doses of 0.3–5.0 mg/m^2 day × 5 i.v. were given to 18 children with leukemia and solid tumors. Toxicity included nausea, vomiting, leukopenia, thrombocytopenia, and transient minor abnormalities in hepatic and coagulation function studies. The leukopenia observed in leukemia patients was transient and not associated with bone marrow hypoplasia. However, leukopenia was more pronounced in solid tumor patients and was associated with a delay in recovery that did not always permit retreatment at 3–4 week intervals. For this reason Phase II studies are in progress at doses of 3 mg/m^2/day × 5 in solid tumors and 5 mg/m^2/day × 5 in leukemia. Antitumor effects observed were reduction in blast counts and organomegaly in two cases of ALL and two with AML.

Iphosphamide (NSC-109724) is a cyclophosphamide analogue that is being investigated because of its superior cytostatic action in the leukemia L1210 system. In addition, iphosphamide is also active in the Lewis lung, Ehrlich ascites, and Yoshida sarcoma systems. Iphosphamide appears to have many characteristics in common with cyclophosphamide, i.e. toxicities (dose-related, reversible leukopenia with relative platelet sparing, nausea, and cystitis), forms of administration (i.v. or p.o.) and range of tumor activity in man. The initial German studies with single large dose therapy (100–150 mg/kg) yielded reports of high activity in oat-cell tumors of the lung, ovarian cancer, breast cancer, and lymphomas.

In the United States, clinical trials with iphosphamide were performed at the NCI-VA Medical Service in collaboration with Roswell Park Memorial Institute [11]. The Phase I trials began at a single dose of 200 mg/m^2, which was escalated in 11 steps to 5000 mg/m^2 with doses repeated every 3 weeks. At the highest dose, patients received either their first or second course with acetylcysteine bladder irrigation. Nausea, vomiting, and hemorrhagic cystitis began at doses above 1700 mg/m^2. At 500 mg/m^2 cystitis occurred in 60% of patients, leukopenia in 50% and thrombocytopenia in 15%.

Ahmann et al. [1] at the Mayo Clinic performed a Phase II evaluation of iphosphamide in breast cancer using a dose schedule of 4 g/m^2 by 4-h infusion every 3 weeks. Four of 20 patients responded to iphosphamide as compared to ten responses among 20 cases in a concomitant combination control group. The toxicity included gastrointestinal effects in all cases, and parenteral fluids were needed by many. Cystitis was noted in virtually all patients and was severe in half of them. A white cell count below 300/mm^3 was observed in 17 of the 24 cases treated with the single agent. Thus far, this analogue has not proven to be superior to its parent compound.

Soluble Baker's antifol (NSC 139105) is a triazine

antifolate placed in Phase I clinical trial because of its high antitumor activity against certain transplanted rat neoplasms and its ability to enter the cerebrospinal fluid in dogs.

Recent studies indicate that poor transport into L1210 cells may explain its lack of efficacy against this experimental tumor. A correlation exists between the ability of the agent to inhibit DNA synthesis in vitro as measured by the uptake of ^{3}H-deoxyuridine incorporation into DNA, and its activity against certain mouse and rat tumors. Studies in human leukemia cells in vitro suggest potential antitumor effects in vivo, assuming that metabolic desposition is not significantly different than in mice, rats, and dog [81]. In vitro tests of cells from patients with acute leukemia and solid tumors show sensitivities to Baker's antifol that are similar to methotrexate with 80–90% inhibition of DNA by 10^{-5} M levels of triazenate [80].

Fifty-seven patients with advanced disease have been treated in a Phase I study at M.D. Anderson Hospital [75]. They received 128 treatment courses at doses ranging from 30–250 mg/m^2/day × 5 i.v. repeated every 2–3 weeks. No biological effect was observed after 20 treatments at doses below 67.5 mg/m^2/day × 5. At higher doses, dermatitis of varying severity was observed in 18% of the cases, mucosities and gastrointestinal side effects in 19%, and myelosuppression in 23%. Antitumor effect was seen in three of ten with adenocarcinoma of the lung, two of 13 with adenocarcinoma of the colon, one of three with adenocarcinoma of the breast, and in one case each with adenocarcinoma of the bladder and synovial sarcoma. Most of the responses occurred at doses of 100–150 mg/m^2/day × 5.

Diglycoaldehyde is the periodate oxidation product of the purine nucleoside, inosine, in which carbons No. 2 and 3 of riboside ring have been oxidized to formyl groups with resultant cleavage of the ring.

Diglycoaldehyde, while only marginally active in Lewis lung carcinoma, has impressive activity against leukemia L1210, leukemia P388, and leukamia AKR. The drug also interferes with the immune response to sheep red cells in mice.

Studies in leukemia L1210 implanted i.p. in rodents show that the maximum increase in lifespan (301%) occurred on a daily × 9 i.p. schedule. With i.v. drug the increase in lifespan was only 32%, although a lower optimal dose was used. These studies suggest that daily administration over a number of consecutive days may be an especially appropriate treatment schedule.

Kaufman and Mittelman [48] have evaluated diglycoaldehyde in 40 patients using discrete esclating doses ranging from 30 mg/m^2 to 3 g/m^2 day × 3–5. Renal and hematologic toxicity were encountered in patients receiving 1.5 g/m^2 or more. Renal toxicity consisted of tubular damage and was reversible when therapy was stopped. Hematologic toxicity was Coombs' positive anemia, mild leukopenia and thrombocytopenia, and elevated thrombin times. The recommended safe regimen for Phase II studies is 2 g/m^2/day × 3 repeated monthly. Objective responses were seen in three of 20 patients who received 2 g/m^2 or more (seminoma, sarcoma, and oat-cell carcinoma). Control of previously resistant hypercalcemia was achieved in one patient each with lung cancer, renal cell carcinoma, and breast cancer.

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Received December 5, 1977