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Schedule and Dosage Modification of a Cyclophosphamide, Hexamethylmelamine, Doxorubicin, Cisplatin Combination Chemotherapy Regimen for Refractory Ovarian Cancer

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Abstract—*A cyclophosphamide, hexamethylmelamine, doxorubicin and cisplatin (CHAP II) regimen produced median survival of* 15 *and* 17 *months. All patients had prior chemotherapy,* 26 *with cisplatin in the former group, and* 27 *without cisplatin in the latter group. Treatment employed both a novel sequential schedule of cisplatin (usually in the evening)* 24 h *before cyclophosphamide–doxorubicin and novel stepwise escalation, first of doxorubicin, then of hexamethylmelamine until either nadir white blood counts fell to* 1000–1500/mm^3 *or platelets to* 75,000–100,000/mm^3. *Compared to prior Mount Sinai experience: (i) survival was significantly improved; (ii) with and without prior cisplatin, response rates approached a significant improvement,* 12% *and* 29% *complete and* 24% *and* 35% *partial. Five of seven additional patients with progression during unmaintained remission also responded, two with pathologically complete remissions. Findings suggest: (i) the importance of maximum dose intensity in ovarian cancer treatment; (ii) the responsiveness of patients failing first line treatment to dose intensive treatment; (iii) the possible importance of schedule, and sequential or circadian timing of cisplatin, and other drugs; (iv) and testing revised clinical criteria of resistance to drugs.*

INTRODUCTION

THE CHAP II regimen for patients with ovarian cancer, failing prior chemotherapy, consists of cyclophosphamide (CYC,C), hexamethylmelamine (HMM,H), doxorubicin (ADM,A) and cisplatin (DDP,P). It differs from preceding Mount Sinai regimens [1].

DDP was given on day 1, 24–36 h before both ADM and CYC. Friend leukemia cells undergo progressive late morphological changes, including giant cell formation. These observations suggest that susceptibility to additional drugs may increase with sequential treatment as these changes occur [2]. The utility of DDP preceding ADM has recently been confirmed [3].

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The dosage intensity of ADM and HMM were increased 60% and 100% respectively, until patients had either a nadir white blood or platelet count of 1000–1500/mm^3 or 75,000–100,000/mm^3 following every course of therapy, thereby maintaining increased dosage intensity.

Parallel studies support development of the CHAP combination. Intensive CHAP regimens produce five of the six best rates of response for ovarian cancer patients and HMM produces a demonstrable dose–response relationship [4]. Each drug, used alone, can produce complete responses after patients fail prior chemotherapy [5].

MATERIALS AND METHODS

Fifty-three patients were registered between December 1979 and December 1983. Eligibility requirements included: (i) histologically proven epithelial ovarian carcinoma; (ii) progressive disease during active treatment; (iii) normal (recovery of) hematological parameters; (iv) absence of infection or any other factor which increases the risk of chemotherapy; and (v) consent.

Treatment regimens, schedules and dose escalation/de-escalation

DDP was given as a 15 min, 50–100 mg/m^2 (minimum dosage of 100 mg), infusion after intravenous fluids, diuretics and antiemetics. DDP treatment was usually given in the evening. On day 2, the patient was given ADM 30 mg/m^2 and CYC 500 mg/m^2 (with hydration), and on day 3, began both HMM 50 mg/m^2 T.I.D. and pyridoxine 50 mg by mouth T.I.D.

As shown in Table 1, treatment began at level I: ADM 30 mg/m^2, HMM 150 mg/m^2 for 7 days for patients with age greater than 70, or prior radiotherapy, or prior clinically life-threatening complications of chemotherapy, or performance status (PS) of ≥2. Other patients began at level II with ADM 50 mg/m^2. Dosage was escalated to level III if nadir white blood count was >1500/mm^3 and platelets >100,000/mm^3 and other toxicity, absent or mild; HMM and pyridoxine were given for 14 days. Rarely, CYC was next increased in 20% increments until the nadirs were achieved.

Table 1. *Secondary therapy: dosage schema*

Drugs Q 4 W	Dosage levels in mg/m^2 I	II	III
Cisplatin day 1	50	50*	50
Cyclophosphamide day 3	500	500	500†
Adriamycin® day 3	30	50	50
Hexamethylmelamine day 3	150 × 7	150 × 7	150 × 14

Begin poor risk patients at level I: age older than 70, prior radiotherapy, performance status 2 or worse. Begin others at level II. Escalate to next level if nadir white blood count is greater than 1.5 × 10^3/l, and nadir platelets greater than 100 × 10^9/l and non-hematologic toxicity is less than grade 3.
*DDP calculated on the basis of minimum surface area of 1.5 m^2.
†Escalated to 600 mg/m^2 if Adriamycin® and hexamethylmelamine fails to produce limiting nadirs.

As shown in Table 2, an intensive effort was made to continue DDP and HMM without interruption. They may have been unnecessarily underutilized in earlier studies [4]. CYC and ADM were reduced 25% for white blood counts of less than 2500/mm^3 on the day of treatment. If platelets were less than 80,000/mm^3, all medications were omitted until recovery. Based on immediate prior nadir counts, CYC and ADM were reduced 25% for white blood or platelet counts of less than 1000/mm^3 or 50,000/mm^3 respectively; if white blood count was below 500/mm^3, HMM was also reduced 25%. If platelets fell below 25,000/mm^3, DDP was also reduced 25%.

Infection prophylaxis

Patients older than 65 were given a double strength trimethoprim sulfamethoxazole preparation T.I.D. when the white blood count was below 750/mm^3. Patients were examined twice a week during the nadir period, and physicians reinforced instructions regarding avoidance of trauma and infection.

Definitions and analytic methods

Definitions and analytic methods were those described earlier in this series of trials [1]. Analyses used both Pearson's chi-square statistics and two-tailed Fisher's exact tests to examine response. Kaplan–Meier estimation methods and Breslow's extension of the generalized Wilcoxon, and log-rank tests served to compare survival. Cox regression served to test on-study characteristics for prognostic relationships to response and survival. Death due to any cause was considered as progression. CHAP II findings were compared to cumulative findings in preceding Mount Sinai studies of DDP, in patients failing chemotherapy [1] both with and without including the current trial's 'ineligible' patients. An additional review was conducted before final analysis in order to identify any patients differing from those in the preceding studies.

Table 2. *Secondary therapy: dosage modification schema*

	Day 1 of next cycle*†				Nadir of last cycle					
	WBC & PLT		WBC & PLT		WBC & PLT		WBC & PLT		WBC & PLT	
Drugs	>3.5	>100	>2.5	>80	>1.0	>50	>0.5	>25	<0.5	<25
Cisplatin	100		100		100		100	75	100	75
Cyclophosphamide	100		75		100		75	75	75	75
Adriamycin®	100		75		100		75	75	75	75
Hexamethylmelamine	100		100		100		100	100	50	50

All counts as 10^9/l.
*If white blood count less than 2.5 and platelet greater than 100, the patient was treated with cisplatin alone.
†If platelet less than 80, all medications were omitted until recovery.

Treatment was continued until either disease or toxicity prevented treatment, except in the case of third-look pathologic complete remission.

Cardiac evaluations

Cardiac ejection studies were recommended after every 100 mg/m^2 increase in the total dosage of ADM, beginning at a total dosage of 300 mg/m^2, and ADM was given as long as these were both more than 50% and within 15% of baseline. DDP was given with mannitol and diuretics in spite of worsening creatinine clearance, even rarely creatinine levels of 4 mg. DDP was discontinued for neuropathy, only when it first affected the hands. HMM was given in any way possible: lower dosage, continuation of dosage after day 14 to complete the total dose, and unequal, evening, fractionation of dosage.

RESULTS

Patient characteristics for ideal eligible patients with full information (Table 3) are similar in frequency to those found in prior studies [1], except that there are slightly more PS-0 patients and more patients with poorly differentiated tumours. More patients without prior DDP tend to have PS-0-1 and fewer patients have PS-3-4. Two-thirds were stage III, one-third were stage IV. Distribution of age and tumor size is similar. The majority had large tumors and the remainder were evenly distributed between 2–6 cm and <2 cm sized tumors. Only the number of patients with prior extensive DDP combination chemotherapy is increased significantly.

Table 3. Characteristics of patients failing prior therapy

Characteristics of patients with prior classic failure	Failing standard therapy No.	%	Failing cisplatin therapy No.	%
Total	17	100	17	100
Age				
<50 years	6	35	5	30
50–59 years	6	35	6	35
≥60 years	5	30	6	35
Performance status				
0	7	41	4	23
1	4	24	3	18
2	4	24	4	23
3	0	0	3	18
4	2	11	3	18
Stage				
III	10	59	10	59
IV	5	29	5	29
Unknown	2	12	2	12
Residual disease				
>1 to ≤2 cm	3	18	2	12
>2 to ≤6 cm	2	12	3	18
>6 cm or unknown	12	70	12	70

Six patients were ineligible: two were never given HMM, two had Brenner tumors and two had ovarian sarcomas. Six patients had insufficient documentation, although they were probably eligible. Analyses were not substantially different with or without including these 12 patients.

Response

The frequency of response for 17 ideally eligible patients failing non-DDP regimens was: 29%, five, complete responses; and 35%, six, partial responses. Compared to prior Mount Sinai studies, CHAP II doubled complete response, which was 8% (6–12%); 32% (21–43%) had partial response; 20% stable disease and 30% (16–37%) progressive disease in patients with no prior DDP [1]. For 17 ideally eligible patients failing a DDP-containing regimen, complete responses were 12%, two, and partial responses were 24%, four, significantly improved compared to prior studies, where only one of eight failing DDP responded [1].

Each on-study characteristic: PS, age, number of prior drugs, and size of residual tumor was independently associated with frequency of response as in the prior studies (not shown) [1]. Compared to historical therapies, this approach tended to but did not achieve significant response improvement in several subgroups (not shown).

Survival

Survival was significantly better than in prior Mount Sinai trials with or without evaluating the outcome of the ineligible patients (Table 4, Fig. 1).

Median survival for the 53 patients was 16 months, compared to the prior 6–7 months. At 1 and 2 years after starting therapy, 65% and 32% respectively were still alive. In prior studies, 1-year survival was less than 20% overall, 26% in the best prior, CHAP I, study; 2-year survival was less than 10% overall, 15% in the CHAP I study.

Median survival was 17.6 months for the 27 patients with prior treatment with DDP. The 17 measurable patients include three formerly stable patients, seven with unmaintained remission, and three considered as either ineligible or having incomplete information.

Median survival was 15.8 months for the 26 patients without prior DDP. This includes 17 measurable and nine considered as either ineligible or having incomplete information (Fig. 2).

Survival was significantly better than with prior regimens (Table 4). Findings were also clear cut in patient subgroups with: symptoms and partially bedridden; both young and, especially old age (Fig. 3); both small and large tumor size (Fig. 4); and both few or many prior drugs (Fig. 5).

For the seven patients with recurrence of disease during a period without chemotherapy after complete pathologically proven remission, CHAP II produced: two (29%) remissions proven pathologically complete and three (43%) partial remissions. One patient had early progression. Patients survived 8, 11, 16, 17, 19, 21 and 40 months. Complete responders relapsed again, during unmaintained remission.

In three symptomatic patients with stable large tumors while undergoing therapy with another DDP-containing regimen, CHAP II produced one complete and one partial response. Patients survived an additional 3, 14 and 22 months. Both survival patterns are similar to the overall group given CHAP II.

CHAP II toxicity

Clinical complications were rare, other than malaise at the time of nadir blood counts and a transfusion requirement for one-third of the patients. Nadir blood counts were objectives of treatment and not examined as toxicities. There were two instances of brief infection (one of these, a patient with 4+ ascites, had peritonitis without bowel perforation); Grade 2 neuropathy, 8%. There were no instances of bleeding due to thrombocytopenia.

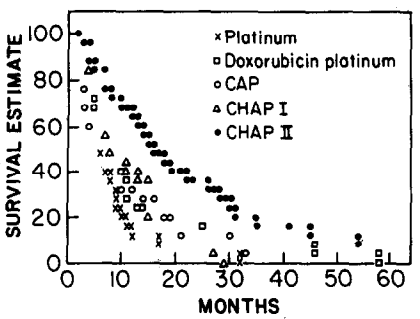


Fig. 1. Survival findings with five consecutive Mount Sinai salvage trials: cisplatin, doxorubicin–cisplatin, cyclophosphamide–doxorubicin–cisplatin, hexamethylmelamine–cyclophosphamide–doxorubicin–cisplatin and CHAP II.

Table 4. Survival by treatment

Treatments		No.*	Median survival (months)	Wilcoxon	Log-rank
Platinum		25	7		
AP		43	7		
CAP		49	8		
CHAP		20	8		
CHAP II		53	16	0.0002	0.002
Prior DDP–CHAP II		26	15		
No prior DDP–CHAP II		27	17	0.531	0.911
Age					
<50	Others	30	6		
	CHAP II	17	17	0.06	0.03
50–59	Others	50	7		
	CHAP II	15	30	0.003	0.004
≥60	Others	57	7		
	CHAP II	21	15	0.005	0.02
Performance status					
0–1	Others	20	18	0.12	0.17
	CHAP II	29	20		
≥2	Others	116	6		
	CHAP II	17	10	0.02	0.007
Tumor size					
<5 cm	Others	25	7		
	CHAP II	28	28	0.028	0.030
≥5 cm	Others	112	7		
	CHAP II (NM)	25	14	0.002	0.011
Number of prior drugs					
1–2	Others	86	8		
	CHAP II	42	17	0.001	0.001
>3	Others	51	6		
	CHAP II	11	15	0.005	0.002

Others combined results = P, AP, CAP, CHAP; P = cisplatin; A = doxorubicin; C = cyclophosphamide; H = hexamethylmelamine; NM = included not measurable, diffuse carcinomatosis.

*All patients including ineligibles/incomplete preclinical information.

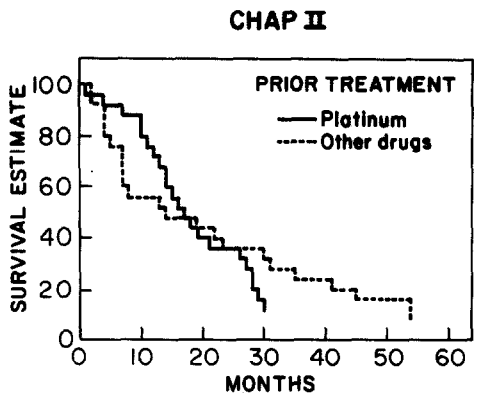


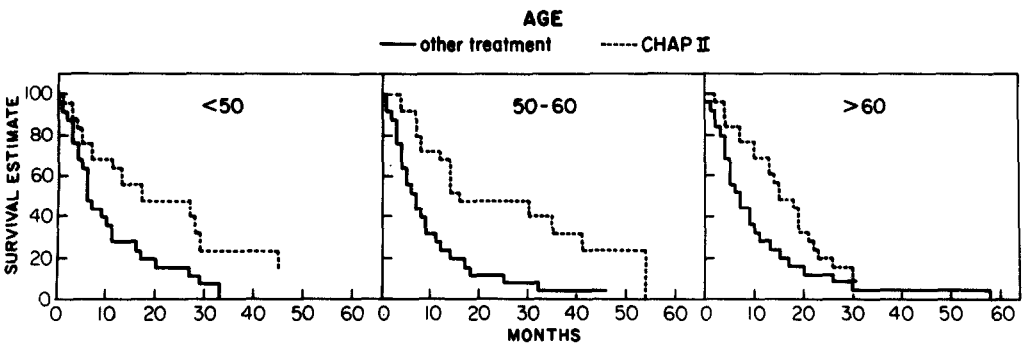
Fig. 2. Comparative survival findings with the CHAP II salvage trial as a function of prior treatment with cisplatin (standard dosage vs. none) demonstrating equal efficacy of CHAP II in spite of prior treatment with cisplatin.

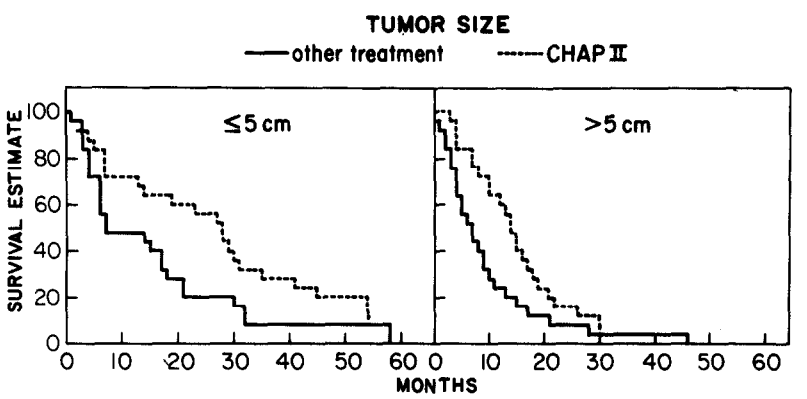
There were two instances of mild clinical congestive heart failures due to ADM which benefited from medical treatment. There were two instances of reversible hepatitis of unknown etiology.

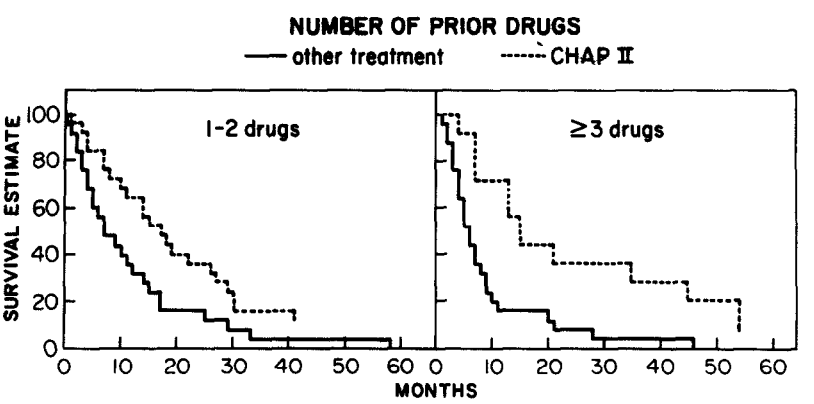
DISCUSSION

Given the limitations of sequential non-randomized trials, the CHAP II regimen improved survival, in spite of using many drugs which had already failed both in the same patients and in earlier studies [1]. These findings challenge current assumptions concerning both the bleak prognosis for median survival after failure of initial therapy, and some definitions of resistance to chemotherapy.

Other causes for improved survival seem unlikely. There was no perceptible change in patient charac-







Figs 3, 4 and 5. Survival findings comparing CHAP II and five earlier Mount Sinai salvage treatments in groups defined by on-study characteristics: age (<50, 50–60, 60+) [3], *tumor size* (<5 cm *vs.* 5 cm) [4] *and number of prior chemotherapy drugs* (1–2 *vs.* 3 *or more*) [5].

teristics, supportive care practices, size of tumor or earlier diagnosis of primary treatment failure. There was no increased in the use of second debulking surgery, CAT scan or tumor assays.

Changes in dosage intensity, circadian timing, and schedule or some combination of these may allow clinically useful re-application of drugs which have already failed. This finding has heretofore been limited to very intensive DDP regimens [6–8]. CHAP II tended to produce a better (34%) frequency of response than the 20% observed earlier, when the dosage of DDP was doubled to 100 mg/m^2 [6, 7], and one comparable to the 35% achieved by increasing DDP to 200 mg/m^2 [8]. Unlike the two- or four-fold larger dosages of DDP, CHAP II appears to produce longer durations of response and survival, and also to be substantially less neurotoxic [6–8]. Few alternative treatments are either equally effective or less toxic than CHAP II.

CHAP II produced complete regression of tumors which recurred after clinicians stopped original treatment. Pathologically proven (third look) complete remissions should not be considered durable. Additional consolidation efforts deserve testing, after a potent debulking regimen such as CHAP II reduces the size of tumors.

There is reason to reconsider clinical criteria of biochemical–pharmacological resistance. Neither 'large tumors' during 'intensive and prolonged therapy' nor relapse during unmaintained remission necessarily predict resistance to the same drugs. Intensive or novel schedules may produce benefit with the same drugs. It follows that this is also true of occult residual tumors present after 6–12 courses of therapy.

In the stable disease group, two of three patients achieved clinical response, one a complete remission. Early changes in dose and schedule are testable alternatives to abandoning best drugs.

Tumor volume probably orders the chance of achieving a second response within several subgroups, too often, falsely assumed to be biochemically resistant (Table 5). A requirement for more sensitive tests, in order to detect tumor growth, provides indirect evidence of small size. These may reflect quantitative difference in tumor volume, which will have prognostic significance for response and survival. Evidence of stable disease or minor improvement presumably also increase the chances of a response with new schedules. Intensity and duration of prior therapy may be additional prognostic variables, but, as shown in Fig. 2, not in all circumstances in the 0–50 mg/m^2 cisplatin dosage range.

Sequential treatment produces both absolute time related biochemical changes and circadian changes. These can improve drug interactions by several different mechanisms, which may occur

Table 5. Patients sometimes incorrectly considered refractory to prior chemotherapy

1. *Second-look after complete or partial response*
   - i Cytology positive only
   - ii Small residual only
   - iii Large (subclinical) residual
     - (a) Debulked, not debulked at second-look
     - (b) Nodes also involved
2. *Relapse detected during unmaintained complete remission*
   - i Marker OC 125 rises; low assay (only); high assay (only)
   - ii Sensitive 'X-ray' tests
   - iii Physical examination: symptomatic (early); symptomatic
3. *Elective crossover for anticipated 'poor' prognosis (response)*
   - i Clinical response complete
     - (a) Marker OC-125 falls too slowly or (b) markers plateau
   - ii Partial response too slow
     - (a) Sensitive X-ray tests, (b) physical examination
   - iii Tumor decreases but plateaus
     - (a) Sensitive X-ray tests, (b) physical examination
   - iv Stable disease after 1–2 cycles
     - (a) Sensitive X-ray tests, (b) physical examination
   - v Stable disease after 3 or more cycles
     - (a) Debulked again, (b) small residual, (c) large residual
4. *Early progressive disease during therapy*
   - i Assay rises
   - ii Sensitive X-ray tests
   - iii Debulked again (electively)
5. *Isolated sites of failure for supplementary therapy*
   - i Peritoneum (intraperitoneal)
   - ii Liver (resection)
   - iii Central nervous system (radiotherapy, intrathecal)
6. *Standard progression large tumor on physical examination*
   - i During low intensity therapy
   - ii During full dosage therapy
     - (a) Less than 3 cycles, (b) more than 3 cycles

Higher number or letter indicates decreasing likelihood of responsiveness.

simultaneously with the CHAP II regimen. The former changes the cell membrane and endoskeleton as well as the cell cycle and intracellular chemistry (biochemical modulation) [2, 3, Bruckner unpublished]. The latter alters the delivered dose intensity by increasing host resistance and also changes tumor sensitivity [9]. It would require surface modeling trials to identify optimum timing for a given combination in man.

The most successful application of CYC–DDP to date also (inadvertently) involved pretreatment with DDP; CYC was delayed until the fourth day of a 5-day course of DDP [10]. Three of the most successful primary treatment regimens appear to utilize sequential treatment rather than prohibitively toxic doses of DDP [10–12]. CHAP II also improved survival in a primary therapy trial; median survival was 43 months [12].

In the current study, optimum compliance creates an overall trend toward improved survival (not

shown). Too many potentially confounding factors create small subgroups and prevent meaningful analyses of either schedule or dosage intensity.

CHAP II illustrates a new safe strategy for dosage intensification. Conventional past dosage intensity efforts clearly did not provide maximum safe feasible treatment. Stepwise escalation must not be subverted to deliver too little drug, too slowly. Rapid escalation and high-dose modification thresholds allow many patients more drug than initially intensive treatments. This may be ideal for intensive tests of drugs whose efficacy is incompletely proven. Following the preliminary analysis of CHAP II [13], confirmed herein, Mount Sinai breast cancer investigators extended application of escalation, with ADM alone, to more severe end points than in CHAP II; this substantially improved both response and survival [14].

HMM may contribute to the effectiveness of combination chemotherapy when dosage intensity is optimum [8]. The successful use of HMM may require finding a dose intensity 'window' to balance its contribution to a regimen against both DDP dosage intensification's positive effects and DDP's negative side-effects. This trial gave priority to delivering HMM in greater intensity than in past studies. Success demonstrated in subsequent trials supports a role for HMM in the treatment of ovarian cancer [15, 16].

The findings challenge both definitions of resistance to chemotherapy and use of conventional dosage schedules. These testable new methods of dosage intensification and schedule modification are applicable to other neoplastic diseases.

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