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I

ANTITUMOUR TREATMENT

The development of combination therapy involving camptothecins: a review of preclinical and early clinical studies

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CANCER
TREATMENT
REVIEWS

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INTRODUCTION

Camptothecin analogues are family of anticancer
agents with a unique mechanism of action, which is
the reversible inhibition of DNA topoisomerase I
(1, 2). DNA topoisomerases are essential nuclear enzymes involved in multiple functions such as chromosomal recombination, DNA repair, tran-scription and chromatin assembly. Topoisomerase! inhibitors exert their cytotoxic action through the stabilization of the topoisomerase IDNA complex, the so-called cleavable complex. This results in col-lision of the DNA replication fork, finally leading to irreversible DNA double-strand breaks and cell death (3, 4). Topoisomerase I inhibitors are of great clinical interest because of their unique mode of action, their important antitumour activity as single agents in a broad spectrum of tumour types (5-30 and the high expression of the enzyme in various human tumour types (31-34). In addition, topo-isomerase I inhibitors may also interfere with the processes involved in DNA repair (35-37). The latter renders them attractive for further investigations of combination therapies, especially involving those with DNA-damaging agents.Preclinical thes.iiay revealed synergisrn...between. tqpoisorneraI in-hibitors and drugs such as!?spjatin, topoisomerase U inhibitors and paclitaxel in a number of different human cancer cell lines and xenografts.
reviews the developn cLckizijtiqntherapy
ith topoisomeras. I inhibitors with a focus on
the two topoisomerase I inhibitors [irinotecan and

Cl!3

’CH3

(a)
H3CH2C - -

ONCH2CH3

0i0X
;.’rdo’

(b)
H3CH2C - -

Figure I Chemical structures of (a) topotecan and (b) irinotecan (CPT- i I).

topotecan (Figure 1)] that are at present registered
IöiElffi1cal use.

PLATIN DERIVATIVES

Prominent clinical activity has been demonstrated
for topotecan and irinotecan in several malignancies

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in which platin derivatives are also highly effective.
The ability of caniptothecin analogues to inhibit
topoisomerase I mediated DNA functions suggests
they might interfere with processesinvolved in DNA
repair and enhance cytotoxicitywhencombined with
DNA-damaging agents. The different toxicity pro-files of platin derivatives and topoisomerase I in-hibitors further support the potential use of these agents in combination.

Preclinical studies

Interactions of topoisomerase I inhibitors with platin derivatives have been studied in vitro and in vivo. The combination of irinotecan with cisplatin(CDDP) was synergistic in human small-cell King cancer (38, 39), oesophageal cancer (40), and ovarian cancer (41,) cell lines, in the human T-cell leukaemia cell line MOLT-3 (43) and in a human tumour xenograft of bladder cancer (44). Additivity was observed in the human ovarian cancer cell line 2008 (45) and in human tumour xenografts of oesophageal, gastric
and colon cancer (46). Also, for the combination of topotecan and cisplatin the interaction varied with
the cell lines examined. S er m was observed in

2- tera o , g oma, ovarian cancer, small-cell lung cancer and non-small-cell lung cancer lines
(47-51) and in an IGROWI tumour xenograft model
(49).
44’ Bissery et al. studied the combination of irinotecan P with oxaliplatin in human osteogenic sarcoma xeno-grafts and found only an additive effect when both
drugs were administered simultaneously (52).
Sequence dependence of the cytotoxicity of the com-
bination of topoisomerase I inhibitors and platin derivatives was also studied by various other
groups. Rowinsky et al. found no sØquence-de-pendent difference in cytotoxicity for cisplatin and topotecan in the A 549 human lung cancer cell line (50). Maliepaard et al., however, observed a strongly synergy

when topotecan or pte Tiipxecede4Jy.Jhe.. p1tiWder1vÆtiTe(42). In contrast to the above-men-d’OstØäsarcoma model data, the combination
of irinotecan and oxaliplatin studied in an FIT 29 human colon carcinoma cell line demonstrated syn-ergism when the drugs were given simultaneously (52, 53). Supra-additivity in the model was found with any sequence of administration (54).
The mechanism of interaction between the topo-isomerase I inhibitor and cisplatin was studied by Zeghari-Squalli et al. and Goldwasser et al. (54, 55). The topoisomerase I inhibitor delayed,the reversal of CDDP-induced DNA interstrand cross-links (ISCs) without modifying the formation of ICSs (53-55). No alteration in cleavable complex formation or

reversion was observed. Simultaneous treatment

prolonged the DNA and RNA synthesis inhibition produced by either drug alone. At higher con-centrations cisplatin (150 pM) enhanced the topo-isomerase I inhibitory activity determined by relaxation of supercoiled Escherichia coli DNA (38), possibly by creating nicks or gaps with 5’-phosphate termini and thereby facilitating the stabilization of the cleavable complexes by the topoisomerase I in-hibitor (56).
These preclinical data on drug interactions be-tween topoisomerase I inhibitors and platin de-rivatives seem to suggest the potential of a sequence-dependent effect. Where observed, synergism might at least partly be explained by interference of the topoisomerase I inhibitor in the repair of CDDP-induced DNA JSCs.

Phase I studies

Phase I studies on the combination of irinotecan

(CPT-11) and CDDP were performed using different schedules of drug administration with a dear focus on fractionated dose schedules for both agents. A once every 3 weeks administration schedule for the two drugs has not yet been investigated. In all studied schedules irinotecan administration pre-ceded that of CDDP. The details of these studies areeceded shown in Table 1 (57-65). Although recent re-commendations are that in such trials phar-macokinetics of both drugs should be studied to exclude interactions, this was only done partly in one of these trials. Moreover, in interpreting these studies we have to bear in mind that, apart from one, they were all performed in Japan. Single-agent study results on irinotecan suggest that Japanese patients may be morsusceptible to irinotecan than,, Caucasians WhŁther this isa result of a friŁphar-macogenetic difference or whether these results re-flect a different approach by the investigatorseflect is unclear. Throughout the studies the major dose-limiting toxicities were neutropenia and diarrhoea. Grade 4 neutropenia was observed in 35% of the patients with the nadir around day 20 (range days 8-29) and recovery in most patients by day 29 (range days 24-39). These neutropenic episodes were com-plicated by fever in only 12% (4% of all patients). By adding G-CSF to schedules with neutropenia as the dose-limiting toxicity, a 33% and 60% increase in dose intensity of irinotecan could be achieved (65, 66). Diarrhoea is a difficult clinical problem associated with the use of irinotecan. It may involve early-onset abdominal cramping and flushes, sug-gestive of release of vasoactive compounds, and delayed-onset secretory diarrhoea. There is a cor-relation with thislate-onset diarrhoea and the bffiary

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TABLE I Phase I studies in the combination of irinotecan (CPT- I I) and CDDP

Day of administration Cycle G-CSF Tumour type Dose-limiting toxicity Recommended dose Reference
interval (m&2-per day)
(weeks)

CPT-I I CDDP CPT-1 I CDDP

I, 8, 15 I 4 NSCLC Diarrhoea, neutropenia 60 80 57
I, 8, 15 1 4 (N)SCLC Diarrhoea 80 60 58
I, 8, 15 I 4 Cervix cancer Neutropenia 60 70 ,59
I, 8, IS I 8, IS 4 NSCLC Neutropenia 60 33- 60
I, IS I 4 Gastric cancer Neutropenia 70 80 61
1,8 1.8 4 (N)SCLC Diarrhoea neutropenia 50 60 62
1-5 4 NSCLC Neutropenia 100 20.-..- 63
I, 8, 15, 21 I, 8, 15,21 6 Various Neutropenia 50 30 64
I, 8, 15 I 4 NSCLC Diarrhoea 80 80 65
I 1-5 4 NSCLC Diarrhoea, neutropenia 160 20. 66

G-CSF, granulocyte colony-stimulating factor, NSCLC, non-small cell lung cancer SCLC small-cell lung cancer

excretion of SN-38, the active metabolite of irino-
tecan, as determined by the extent of SN-38 glucur-.
omdation in plasma (67). The acute diarrhoea
responds to treatment with atropine. Whenever se-
cretory diarrhoea developed, immediate therapy
with loperamide was started, rendering the diar-rhoea manageable. Other side-effects consisted of nausea and vomiting, alopecia and mucositis. Major responses were observed in all treatment schedules in patients with non-small-cell lung cancer, small-cell lung cancer, gastric, head and neck and cervix carcinoma (response rates reported: 35-80%). Al-though the latter data are of limited value in view of the small sample sizes, the combination of irinotecan and cisplatin seems to be highly active. Pharmacokinetics was only studied by Masuda et al. (56) and Sumiyoshi etal. (68). The former observed a marked increase in the mean peak plasma con-centrations and the area under the concentration-time curve (AUC) of SN-38 after a modest increase in the dose of irinotecan, suggesting a potential pharmacokinetic interaction. However, recently the metabolic ratio of the conversion of irinotecan to SN-38 (AUCsN./AUCll) (Figure 2) was considered to be a reliable parameter to determine any phar-macokinetic interaction. Comparison of the meta-bolic ratio of the combination therapy to the single-agents therapy with irinotecan did not reveal any difference, indicating no apparent interaction (69-72). These data lend further support to the re-commendation to include pharmacokinetics in combination chemotherapy phase I studies.
The dose intensity of irinotecan that could be achieved in combination with cisplatin varied from 25-60% of the single-agent dose. Higher dose in-tensities were reached when irinotecan was com-bined with a single administration of cisplatin. As stated, a once every 3 weeks administration schedule

0.04

0.03

0.02

0.01

Range Range
(0.03-0.05) (0.01-&08)

CPT-11 CPT-11
CDDP

Figure 2 Metabolic ratio AUCsN/AUCCII of the conversion of irinotecan to SN-38 in irinotecan single-agent therapy and combination therapy with cisplatin.

for both drugs has not yet been investigated. Further studies on patients in Europe and the U.S.A. have
to be awaited for a better insight in the tolerability
of the combination of irinotecan and cisplatin. yin- -
desine was also found to be feasible. Dose-limiting toxicities again consisted of neutropenia and diar-rhoea. The recommended doses for phase II studies
are either irinotecan 37.5 mg/m2 per day days 1 and
8 in combination with cisplatin 100 mg/rn2 day I and vindesine 3mg/rn2 per day days 1 and 8, or irinotecan 80mg/rn2 per day days 1 and 8 combined with cisplatin 60 mg/m’ day 1 with the same dose of vindesine (73).
Sugiura et al. studied the combination ofçn. and carboplatin (74). Carboplatin was administered dose of 300 mg/rn2, with escalating
doses of irinotecan on days 1, 8 and 15 every 4 weeks. Dose-limiting toxicities consisted of neutro-and thrombocytopenia and diarrhoea. The re-commended dose of irinotecan for phase II studiescommended

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TAKE 2 Phase I studies on the combination oftopotecan and CDDP

Day of Cycle G-CSF Dose-limiting toxicity Recommended dose Reference
administration interval (mg/m2 per day)
(weeks)

Topotecan CDDP Topotecan CDDP

1-5 I 3 Neutropenia. Not feasible 78
thrombocytopenia
1-5 I 3 Neutropenia 1.0 50 79
1-5 I 3 Neutropenia, 0.75 50 50
thrombocytopenia
1-5 1-5 4 Neutropenia Not feasible 80
1-5 I 3 Neutropenia, 1.0 75 79
hyperbitirubinaemia
1-14 c.i.v. I 4 Not yet reached 0.4 a75 81

dv., continuous intravenous infusion.

with this combination is 50mg/rn2 days 1,8 and 15.
Adding G-CSF seemed to enable somewhat higher
doses of irinotecan (75). Cvitkovic et al. studied the
combination of oxaliplatin (L-OHP) and irinotecan
in colorectal cancer (76). L-OHP was given as a 2 h infusion followed by 1 h by irinotecan given over 30 min, once every 3 weeks. Dose-limiting toxicities consisted of neutropenia and diarrhoea. Other side-effects included peripheral neuropathy, nausea and vomiting. Recommended doses for phase II studies are oxaiiplatin 110 mg/m2 in combination with irino-tecan 200mg/rn2. Pharmacokinetic data show not drug interaction. The AUCs of irinotecan SN-38, SN-38G and L-OHP were comparable with single-agent data (77).
Combining topotecan with cisplatin also required considerable-dQse reduction as compared with the single-agent dose. Several schedules of ad-ministration were studied. The details are sum-

marized in Table 2 (50, 78-81). Dose-limiting toxicities consisted of neutropenia and thrombo-cytopenia. Attempts to increase the dose of either topotecan or CDDP only marginally rapidly resulted in unacceptable toxicity. In the study of Miller et al. further dose escalation of CDDP seemed feasible after addition of G-CSF (79). However, in a sub-sequent phase II study using thisschedule inpatients with small-cell lung cancer (extended disease) un-acceptable toxicity was encountered (82). This fact stresses the importance of patient selection, because patients with small-cell lung cancer are more vul-nerable for developing infectious complications in the case of chemotherapy-induced prolonged neu-tropenia. Considering the definition of dose-limiting toxicity in this study, these side-effects could have been expected. In the study performed by Rowinsky
al. no further dose escalation was possible after

400

8
300

1.1200

’ 100

0

day day day

Figure 3 Clearance oftopotecan on day I in sequence topotecan days IS, cisplatin day 5 (T-+C) and cisplatin day I topotecan days 1-5 (C-+T).

and vomiting, diarrhoea, mucositis, fatigue and alo peda. Other organ toxicities were not reported.,hnJ preclinical studies sequence dependence was noted for the combination of CDDP and topotecan. Un-fortunately the potential importance of sequence dependence in the clinical setting has only been
investigated by Rowinsky (50). In their study
topotecan was administered as a 30 min infusion daily for 5 days and cisplatin was given either before topotecan on day 1 or after topotecan on day 5, alternating in the same patient CDDP given before topotecan induced significantly more and severe neutropenia and thrombocytopenia than the al-ternate sequence. Pharmacokunetic studies sug-gested that the differences in toxicity were due in part, to lower topotecan clearance when CDDP pre-
ceded topotecan administration (Figure 3). Also, receded maximal interactions between topoisomerase I-DNA adducts and polymerase molecules involved in repair of cisplatin-induced DNA damage might

addition of G-CSF (50). Non-haematological toxicity (as usually mild to moderate, consisting of nausea

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play a role. In theory this could result in an increase
in both antitumour activity and toxicity due to a decrease in repair, if cells were exposed to alkylating agents early in the course of topotecan treatment. These effects, however, were not measured. Heideman et al. (83) studied the combination of topotecan and carboplatin in paediatric solid tumours. Carboplatin was administered at a fixed target
tinuous infusion 22tecanifor72h, course re-peated every 4 weeks. Dose-limiting toxicity consisted of neutropenia and thrombocytopenia at a topotecan dose of 0.5 mg/rn2 per day. The re-commended dose of topotecan for phase II studies is 0.4 mg/rn2 per day. Pharmacokinetic data could not reveal any interaction between topotecan and carboplatin.
Both the predlinical and clinical data underscore the necessity to evaluate sequence-dependent effects of combination therapy already in phase I in-vestigations. Further investigations are needed to determine whether the sequence causing more side-
effects is also the more potent one. To assess ideeffects any pharmacokinetic interaction between the drugs ad-ministered, in all phase I studies involving com-bination regimens pharmacokinetic and pharmacodynamic data should be collected.

COMBINATIONS WITH OTHER

ALKYLATING AGENTS

In preclinical studies the combination of topotecan with DNA alkylating agents (melphalan, bis-(chloroethyl)nitrosurea and 4-hydroperoxy-cyclophosphamid6) at low-to-intermediate levels of cytotoxicity revealed cytotoxic effects that were less than additive in most cases. However, nearly ad-ditive or synergistic effects were observed with the same drug combinations athigh levels of cytotoxicity (i.e. at?t 90% inhibition of colony formation) 47. The combination of topotecan with cyclo-phosphamide was studied in patients with refractory cancer and patients with refractory leukaemia (84-86). Miller et al. treated patients with refractory leuk-aemia with cyclophosphamide 40mg/kg day 1 followed by a continuous infusion of topotecan days 2-6 at a dose of 1.5 and 1.8 mg/m2 (84). Dose-limiting toxicity had not yet been reached at the time of publication of the abstract. Preliminary data suggest activity of this combination. A different schedule was studied in paediatric patients with malignant solid tumours (85). A fixed dose of cyclo-phosphamide 250 mg/rn2 per day was followed by topotecan in escalating doses, each given as a 30 mm infusion daily for 5 days repeated every 3 weeks. At

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the starting dose of topotecan (0.75 mg/m2 per day) dose-limiting neutropenia was observed. Dose re-duction of topotecan to 0.60mg/rn2 per day alsoeduction resulted in dose-limiting toxicity. Addition of ifi-grastim allowed the escalation of topotecan to the 0.75 mg/ml per day dose level, which is the dose recommended for further phase II studies. However, patients treated at this dose level experienced sub-stantial anaemia and thrombocytopenia requiring platelet transfusions in 531/6 of the courses and red blood cell transfusionsin 50%. Also, 20% of treatment courses at the recommended dose level were com-plicated by febrile neutropenia. Pharrnacokinetic data indicated no alteration of topotecan kinetics. Re-sponses were reported in patients with a Wilms’esponses tumour, neurbiastorna, rhabdomyosarcoma and osteosarcoma. Interestingly, the responding patients were all pretreated with either ifosfarnide or cyclo-phosphamide. Murren et al. combined a fixed dose of cyclophophainide 600 mg/m’ day 1 with escalating doses of topotecan given as a 30 min infusion for five consecutive days every 3 weeks in patients with refractory solid tumours (86). Doses of topotecan ranged from 0.5 to 1.2 mg/rn2 per day. Reversible neutropenia was dose limiting at a dose of topotecan of 1.0 mg/rn2 per day. Other side-effects were an-aemia, thrombocytopenia, fatigue and weight loss. The recommended dose for phase II studies for pre-treated patients is topotecan 0.75 mg/m2 per day days 1-5 without growth factor support and 1.0 mg/m2 per day days 1-5 if G-CSF is added. Cyclo-phosphamide did not appear to alter the phar-macokinetics of topotecan. Significant increases in topoisomerase I concentration were identified in peri-pheral-blood mononuclear cells after the ad-ministration of cydophosphamide on day 1, followed by a significant decrease during the 5 day course of treatment with topotecan. This means that bio-chemical changes in cells induced by exposure to camptothecins can be measured in vivo. These effects can be used to monitor pharmacodynamic inter-actions in combination therapies with camptothecms and to determine the optimal scheduling of this class of agents.
In 24 patients with dear cell carcinoma of the ovary, who progressed during platinum-based chemotherapy or relapsed within 6 months after the end of platinum-based chemotherapy, irinotecan 140 mg/m2 infused i.v. over 4 h on days 1 and 15 was combined with intraperitoneal mitomycin-C 7mg/rn2 on days 1 and 15 every 4 weeks. This schedule was never appropriately tested in a phase I study. Therefore it is impossible to conclude whether patients were appropriately dosed. In 11% of the courses, grade 3 diarrhoea was observed. Other side-
effects were acceptable. Despite the dose issue,ideeffects 11 patients showed a response (87).

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TOPOISOMERASE II INHIBITORS

Preclinical studies

It has been shown in preclinical studies that cross-
resistance to topoisomerase I and II inhibitors is
unusual in resistant cell lines (88, 89). Alterations
in the regulation of one topoisomerase are often compensated by alterations in the other (90). The expression of topoisomerase II is enhanced in topo-isomerase I deficient cells (91) and cell lines with deficient topoisomerase I activity appear to be more sensitive to treatment with topoisomerase U in-hibitors (92). This led to the assumption that the combination of a topoisomerase I and II inhibitor might lead to synergistic cytotoxicity. Preclinical studies on the combination of camptothecins and topoisomerase U inhibitors, however, revealed that their interaction was cell line and sequence de-pendent. Concomitant administration resulted in antagonism in HL-60 human progranulocytic leuk-aemia cells (93), U 251 glioma cells (94), HT-29 human colon cancer cells (95) and SW 480 colon carcinoma xenografts (96). In other cell lines additive or even synergistic cytotoxicity was noted (43, 94, 97). Also, in a firststudy combining 9-aminocampto-thecin with etoposide in human glioblastoma cells a synergistic effect was noted (97). Sequence-de-pendent cytotoxic effects were studied by combining several topoisomerase I and II inhibitors. The out-come varied with the cell lines studied (98, 99). However, when the administration of the topo-isomerase II inhibitors, etoposidc or was preceded by the administration of a topoisomerase I inhibitor in most cell lines and xenografta syner-gistic effect was noted (46, 9jQ1Q This might explained by an increase in topoisomerase U levels observed after inhibition of topoisomerase I (46, 104, 105) and an increase in the S-phase cell population, which might enhance the sensitivity to topoisomerase II inhibition (43, 46, 93, 95, 96, 102). >These results seem to suggest that concurrent ad-ministration of topoisomerase I and U inhibitors is unlikely to be beneficial. Clearly, appropriate clinical studies are required to examine formally whether or not sequential administration of these agents offers any advantage over monotherapy (106).

Phase I studies

Several phase I studies combining irinotecan and etoposide (VP-16) were performed (Table 3) (107-110). The combination of both drugs was only feas-ible with growth factor support, suggesting at least

additive myelotoxicity. Dose-limiting toxicity con-sisted of a combination of neutropenia, thrombo-cytopenia and diarrhoea. Further common side-effects consisted of nausea and vomiting, alopecia, reversible elevation of transaminases and bilirubin. The elevation of transaminases and bilirubin cor-related with the grade of the observed haemato-logical toxicity (107). This may suggest that liver impairment may prolong bone marrow exposure, leading to more pronounced and prolonged myelo-suppressions. Otherwise, liver impairmentmight co-segregate withmyelosuppression as a sign of severe toxicity. Because both drugs are metabolized in the liver, the administration of irinotecan and etoposide on consecutive days may have caused these hepatic toxicities via any drug-drug interaction. Ando et al. investigated the effect of the sequence of drug administration on the observed toxicity (107). Patients were treated with irinotecan days 1-3 fol-lowed by treatment with etoposide days 44 (arm A) or with etoposide days 1-3 followed by irinotecan days 4-6 (arm B). G-CSF was given to all patients daily on days 7-17. No remarkable difference in toxicity was observed between the two treatment arms, although the AUCs of irinotecan and SN-38 were significantly higher when this drug followed the administration of etoposide. In a study com-bining irinotecan and etoposide on days 1-3 a drug interaction was also suggested. C and AUC of etoposide were significantly higher on day 3 than on day 1 (108). Clearly all further studies on the combinations of these two drugs should be par-alleled by pharmacokinetic studies in order to elu-cidate the background of these apparent but unexplained interactions.
The combination of topotecan and etoposide was studied in patientsffthThblidfi sartd in ªtients with haematological malignancies (Table 3) (111-414). In patients with solid tumours the dose limiting toxicity consisted of neutropenia (113, 114). In general, the haematological toxicity encountered was more severe than expected. The AUC of to-potecan correlated with the decrease in white blood cell count (r2=0.65) (114). As expected in view of schedule and known half-lives, topotecan and eto-poside pharmacokinetic parameters were similar to those reported in single-agent studies. Eckardt et al. determined tumour topoisomerase U levels in five patientswith accessible solid tumours (105). Samples were taken before the start of the therapy, after the last topotecan administration and after the last etoposide administration. In one patient with colon cancer topoisomerase U levels were markedly in-creased after administration of topotecan and de-creased again after administration of etoposide. This patient demonstrated a resolution of ascites. In the

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TABLE 3 Phase I studies on the combination of topoisomerase I and II inhibitors

Day of administration Cycle G-CSF Dose-limiting toxicity Recommended dose Reference
interval (mg/m’ per day)
(weeks)

CPT- II VP-16 CPT- I I VP- 16
1-3 4-6 4 + Neutropenia. thrombocytopenia, Not feasible 107
diarrhoea
1-3 I-3 3-4 + Diarrhoea 60 60 108
I 8, IS 1-3 4 + Neutropenia, diarrhoea 80 80 109
70 pretreated 80 110
I, 8, 15 1-3 4 + Neutropenia, diarrhoea 70 80

Topotecan VP- I 6 Topotecan VP- I 6
1-5 6-8 3-4 - Mucositis 1.5 100 III
1-3 civ. 4-8 - Mucositis, diarrhoea, 0.85 100 112
hyperbilirubinaernia
1-3 civ. 7-9 4 - Neutropenia 0.17 pretreated 100 113
1-5 6-12 b.i.d. - Neutropenia 1.0 40 114
P.O.

Topotecan Doxorubicin Topotecan Doxorubicin
1-3 civ. 5 3-4 - Neutropenia 0.35 45 115
1-3 civ. 5 3-4 + Neutropenia, thrombocytopenia 0.75 45 115

CLV., continuous intravenous infusion: p.o. oral1 bid., twice per day.

other four patients no pattern of modulation of
topoisomerase I or II levels was observed.
In patients with acute myeloid leukaernia dose-
limiting toxicities consisted of mucositis, hyper-
bilirubinaemia and peripheral neuropathy (111, 112). Grade 4 neutropenia and thrombocytopenia was seen in all courses. Topoisomerase land IIlevels were measured in leukaemic blasts before and during
the treatment with topotecan. Both levels decreased during therapy compared withpre-treatment values.
No correlation was found between the decline in topoisomerase I and clinical tumour response (111, 112).
. . - Combinations ofjgamtqpwithdoxorcir were also studied. For topotecan this involved a 72 h
ó ntinuous infusion followed by bolus doxorubicin
on day 5. Cycles were repeated every 3-4 weeks (115). Unexpectedly dose limiting toxicity (neu-fropenia) was already encountered at the first dose level but with the addition of G-CSF a further dose increase was feasible. The recommended dose for phase II studies is topotecan 0.35 mg/m2 per day continuous infusion on days 1-3 without G-CSF or 0.75 mg/m2 per day with G-CSF, followed by doxorubicin 45mg/rn2. No alterations in drug clear-ance were found as compared with single-agent data. In ten patients paired bone marrow aspirates were obtained before and after treatment with to-

potecan. In seven of 10 patients, an increase in the proportion of CD341 cells in S phase was noted 24 h after the end of topotecan infusion. This increase may in part be responsible for the unexpected haematological toxicity, because topoisomerase 11

inhibitors such as doxorubicin are most cytotoxic to cells in S phase when the topoisomerase II enzyme levels are the highest (93).
Saotome et al. performed a pilot study on the combination of irinotecan 25mg/rn2 per day given on days 1 and 2 and doxorubicin 40mg/rn2 given on day 3, cycles repeated every 3 weeksin 12 patients with relapsed malignant lymphoma refractory to doxorubicin-containing chemotherapy or relapsing after doxorubicin regimens. Major toxicities included leulcocytopenia (?!:WHO grade 3: 670/6), thrombo-cytopenia (25%), and diarrhoea (8%). Four patients (33.31/6) achieved a complete response (117).
At present, based on the above data, it appears that combining topoisomerase I and II inhibitors is difficult for a variety of reasons. In general these combinations yield much toxicity, especially myelo-toxicity, which renders it impossible to administer enough drug and enough courses of treatment to expect an important level of antitumour activity.

ANTIMETABOLITES

Predinical studies

Because irinotecan and 5-fluorouradil (5-FU) are two drugs active in metastatic colorectal cancer and ir-inotecan exerts its cytotoxic activity in both chemo-therapy-naive and pretreated patients, combination
therapy with 5-FU interestirrgerW
11simultaneous incubation of HT-
29, HCT-8, HT-29R1, HT-29R4 colon cancer, A549

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lung cancer and human T-cell leukaemia MOLT 3
ceIl lines with irinotecan-SN-38 or topotecan and 5-
- FU revealed antagonistic or only additive effects (43,
47, 118-122) as did simultaneous treatment in an
HT-29 colon cancer xenograft model. Sequential in-,
cubation, with 5-FlJ preceding resulted in either antagonism (12O,7l21).r synergism (118,
123) depending on the cell lines studied. In case of jynergisn 5-EU.seemed to augment the ac-cumulation of irinotecan in the cell and to increase topoisomerase I levels (118, 122).When irinotecan incubation preceded usua1y observed (118-120; 124). Irinotecan did not modify 5-FU uptake by the cell. However, the combination of 5-FU and irinotecan induced a higher thymidylate synthase inhibition than 5-FU alone (124). In an HT-29 nude mice xenograft model tumour relapse was preceded by an increase in thynüdylate synthase activity and a decrease in achieved topoisomerase I inhibition (124).
Aschele et al. studied the combination of Tomudex and SN-38 in HCT-8 colon cancer lines (125). Syn-ergism was encountered with sequential short-term exposure with any sequence of administration. How-ever, the magnitude of potentiation was greater when SN-38 was given first and when a higher relative dose of Tomudex was used. Combinations of topotecan and methotrexate or cytarabine revealed cytotoxic effects that were less than additive (47). For irinotecan, antagonism was observed in combinationwithmethotrexate (43). The combination of irinotecan with cytarabine showed a synergistic effect (43).

Phase I studies

Numerous studies were initiated to assess the feas-ibility of the combination of irinotecan and 5-FU. Salz et al. conducted a phase I study on irinotecan administered over 90 min days 1, 8,15 and 22 every 6 weeks

-(126). The first 5-FU and leucovorin were ad-ministered on day 2. On days 8,15 and 22, irinotecan infusion was immediately followed by leucovorin and then 5-FU. For the second 6 week cycle, leuco-vorin was administered first, followed by 5-FU and then irinotecan, which permitted comparison of the pharmacokinetics of irinotecan in the different se-quences of administration. Dose-limiting toxicity was neutropenia. Although diarrhoea was common, it was rarely dose limiting. Other side-effects con-sisted of nausea and vomiting (>grade 2 only in 1/27 patients), fatigue and alopecia. Among the 38 patients with colorectal cancer, six partial responses (169/6) were seen in this predominantly 5-FU-re- - fractory patient population. The recommended dose

for phase II studies is irinotecan 125 mg/m2 in com-bination with 3-FU 500 mg/m2 and leucovorin 20mg/rn2 days 1, 8, 15 and 22, cycles repeated every 6 weeks.
The co-administration of 5-FU had no substantial effect on the pharmacokinetics of irinotecan or SN-38, in contrast with the results reported by Sasaki et al. They suggested that 5-FU reduced the degree of conversion of irinotecan to SN-38, possibly by interference with the function of carboxylesterases that catalyse this conversion (127). However, their pharmacokinetic data were obtained in a relatively small number of patients. Also, the pharmacokinetic data obtained by other investigators revealed no difference in irinotecan kinetics with the co-ad-ministration of 5-FU, whatever the order of ad-ministration (128-130). Benhammouda et al. studied the combination of irinotecan and 5-FU in a three-weekly schedule (130). Dose-limiting toxicity was haematological. The recommended doses for phase U studies are irinotecan 300 mg/rn2 day 1 and 5-FU 375 mg/m2 per day i.v. bolus days 1-5 q. 3-4 weeks. Several phase I studies combining irinotecan and 5-FU different schedules are still ongoing, but the preliminary reported data have not revealed any dose-limiting side-effects (Table 4) (126, 129-135). Thus, these preliminary resultssuggest that the com-bination of irinotecan and 5-FU is well tolerated. Another approach to combine irinotecan and 5-FU consists of the alternating administration of both agents. Two schedules were studied: irinotecan 350mg/rn2 90 min day 1 and 5-FU 425 mg/rn2 im-mediately after leucovorin 20mg/rn2 days 22-26, every 6 weeks (136), and irinotecan 100 mg/m2 weekly x 4 followed by a 2 week rest, after which 5-FU 425 mg/m2 and leucovorin 20 mg/m2 are both given for 5 days, the full cycle repeated every 10 weeks (137). In these alternating regimens similar toxicities were observed to those of either therapy given alone. Overall response rates of 26% (18/70 patients) and 31% (9/29 patients) were achieved in patients with colorectal cancer.
The latter studies add further evidence that irino-tecan can be easily combined with various 5-FU regimens. This has prompted the initiation of a phase ifi study comparing such a combination with high-dose infusional 5-FU alone in patients with colorectal
cancer.

A phase I study on the combination irinotecan and tomudex, another regimen of potential interest in colorectal cancer, was recently completed, but data have not yet been reported (138).
In patients with acute leukaemia, not responsive to standard therapy, the combination of topotecan and cytarabine was studied (139). Topotecan was given as a 30 min infusion daily with cytarabine 1 g/m2 per day, both for 5 days. Oropharyngeal mucositis

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TABLE 4 Phase I studies on the combination irinotecan (CPT- II) and 5-FU and leucovonn

Days of administration Cycle interval Colorectal Dose-limiting Recomended dose Reference (weeks) cancer toxicity (mg/m’ per day)
response
rate

5-FU Leucovorin CPT- I I 5-FU Leucovorin CPT- I

I B, 15, 22 I, 8, 15, 22 I 8, 15, 6 6/38 Neutropenia 500 20 125 126
22

1-5 I 3-4 Neutropenia 375 300 130
2-5 2-5 I Not reached 250 20 200 131
1-7 civ. I 3-4 Not reached 400 ?- 225 132
3-8 civ. I, 15 5/19 Not reached 600 ?: 150 129
1-14 c.i.v. I 3 Febrile neutropenia. 250 350 133
Diarrhoea.
mucositis

I, 24 h I I Weekly x 6 15/24 Diarrhoea 2600 500 80 134
followed by I
week rest
I I I 2 8/31 Not reached 400 bolus 200 200 135
bolus + 22 h 600 civ,
c.i.v.

c.i.v., continuous intravenous infusion.

was dose limiting. Liver function test abnormalities
occurred frequently but in most cases were re-
versible. All patients developed neutropenic fever
that required treatment with broad-spectrum anti-biotics. The recommended phase II dose oftopotecan is 4.75 mg/rn2 per day for 5 daysin high-risk patients (PS 2, or >one prior chemotherapy regimen) and 7.0 mg/m2 per day for low-risk patients. This is three to five times the recommended dose for topotecan as single agent in patients with solid tumours. During therapy the percentage of apoptotic cells in blood and bone marrow was determined, and the cell cycle distribution of the leukaemic cells was studied. The maximal number of apoptotic cells was seen in the blood 48 h after the first administration of topotecan. Patients with a high S-phase fraction either before treatment or following cytarabine were more likely to achieve bone marrow aplasia. This result is in line with the fact that both drugs are most active in S phase.

TAXOIDS

Only limited preclinical data are available for the combination of paclitaxel or docetaxel and topo-isomerase I inhibitors. The combination of irinotecan or topotecan with paclitaxel resulted in less than additive cytotoxicity in several cell lines (47). In breast cancer xenografts a good antitumour efficacy was noted for the combination of irinotecan and docetaxel (140).
Because paclitaxel and topotecan both dem-onstrated activity in women with recurrent and

cisplatin-refractory ovarian cancer, the feasibility of combining these agents was pursued. Topotecan, administered as a 30min infusion days 1-5, was combined with paclitaxel both studied as a 3 h (141) or a 24h (142) infusion. When paclitaxel was given as a 3 h infusion before the administration oftopotecan, dose-limiting toxicity consisted of neutropenia. The recommended dose for phase II studies is paclitaxel 80mg/rn2 day 1, combined with topotecan 1.0 mg/m2 per day days 1-5, cycles repeated every 3 weeks. With addition of ifigrastim, the dose of paclitaxel could be further escalated to 230mg/rn2 in com-bination with the same dose of topotecan.. Dose-limiting toxicity consisted of a combination of haematological toxicity (especially neutropenia) and neuromuscular toxidty. Other non-haematological toxicity was usually mild and included nausea and vomiting, diarrhoea, mucositis, myalgia and ar-thralgia. The other phase I study was performed in patients with recurrent or refractory ovarian cancer, and paclitaxel was given over 24 h combined with topotecan days 1-5, again with cycles repeated every 3 weeks (142). Dose-limiting toxicity consisting of neutropenia was already encountered at the first dose level (topotecan 0.75 mg/m’ per day days 1-5, paclitaxel 135 mg/m2 day 1). Even after addition of ifigrastim no further dose escalation was possible owing to unacceptable haematological toxicity (neu-tro- and thrombocytopenia). The recommended dose for further phase II studies is topotecan 0.75mg/rn2 per day days 1-5 and paclitaxel 135 mg/rn2 with G-CSF support. Non-haematological toxicity consisted of mild nausea and vomiting, mucositis and diar-rhoea. In this study the issue of sequence-dependent

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toxicity was also addressed. No difference in toxicity was observed whether paclitaxel preceded the ad-ministration of topotecan or was given on day 6, after the administration of topotecan. Also, no phar-macokinetic interaction between paclitaxel and to-potecan was observed. Given the magnitude of toxicological differences between the 3 and 24h paclitaxelschedules, particularlywithrespect to neu-tropenia, it seems most appropriate to select the 3 h paclitaxel infusion for further combination studies with topotecan. It results in less myelosuppression and allows higher doses of topotecan and paclitaxel to be combined.
Of concern, in a subsequent phase II study in patients with extended-stage small-cell lung car-cinoma using the combination of paclitaxel as a 3 h infusion with topotecan, unexpected severe haematological toxicity was encountered. Three of the 13 treated patients died of treatment-related sepsis (82). In patients with small-cell lung cancer neutropenic fever and infection are related to the duration of grade 4 neutropenia. Considering the definition of dose-limiting toxicity in the phase I study, grade 4 neutropenia lasting more than 7 days, this toxicity could have been expected in this patient population. Moreover, lung cancer patients are known to be more prone to developing post-ob-struction infections. In view of this, dose levels for further studies should be chosen depending on the patient population and the risk of prolonged and/or febrile neutropenia deemed acceptable. Given the magnitude of the haematological effects, of both the 3 h and the 24 h paclitaxel-topotecan regimens, and the requirement for haematopoietic colony-stimu-lating factor support, further careful evaluation of these regimens is necessary.
Another phase I study assessed the toxicity of the combination of paclitaxel on day 1 as a 3 h infusion with topotecan as a continuous infusion over 14 days once every 3 weeks (143). Dose-limiting toxicity consisted of neutropenia. In pretreated patients the dose recommended for further studies is paclitaxel 135 mg/m’ in combination with a daily topotecan dose of 0.3 mg/m2. In chemotherapy-naive patients further dose escalation is ongoing.
Docetaxel given three weekly was studied in com-bination with irinotecan in a weekly and a three-weekly schedule. Docetaxel 60 mg/m2 given as a 60 min infusion could be combined with irinotecan 250 mg/min’ given over 90 mm, once every 3 weeks. Dose-limiting toxicity was febrile neutropenia. No pharmacokinetic interaction between the two drugs was observed (144). In the study combining irino-tecan on days 1,8 and 15 with docetaxel day 2 every 4 weeks(145) dose-limiting toxicity was encountered at the dose level combining docetaxel 50 mg/rn2 and irinotecan 60mg/rn2 and consisted of neutropenia

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and diarrhoea. Additional dose levels are under

study to determine the recommended dose of this combination for further phase II studies.

PHASE II STUDIES

The results of published phase U studies in which combination chemotherapy with topoisomerase I inhibitors was used to treat patients with solid tumours are summarized in Table 5 (87, 146-153). Response rates of 31-541/6 have been reported in previously untreated patients with advanced non-small cell lung cancer using the combination of cisplatin with irinotecan.. The major side-effects con-sisted of myelosuppression (>grade 3: leukopenia 13-23%, neutropenia 22-46%, thrombocytopenia 12-18%) and diarrhoea (;agrade 3: 17-25%) (146, 147). A high percentage of patients required reduction of the irinotecan dose especially as a result of non-haematological toxicity. This regimen also seems to be highly active in patients with small-cell lung cancer, yielding an overall response rate of 84% and a complete response rate of 29%. During the latter study the dose of irinotecan in the first course had to be reducedbecause ofsevere haematological toxicity, diarrhoea and/or liver toxicity in three of the initial 10 patients (150). High response rates have also been achieved using the combination of CDDP and irinotecan in patients with gastric carcinoma (151). In first-line therapy a response rate of 59% was noted; in second line this was 27%. The median duration of response was 118 days (range 41-253 +days). The encountered toxicity was ac-ceptable (grade 4 neutropenia 221/6;;-> grade 3 diar-rhoea 7%). The same combination used as first-line chemotherapy also yielded a response rate of 68% in patients with recurrent or advanced cervical cancer (153). A phase II study using the same combination in patients with relapsed ormetastatic ovarian cancer revealed a response rate of 541/6 (152). Because of neutropenia, the administration of irinotecan on day 15 was skipped in 31% of the patients receiving irinotecan at 60mg/rn2. Therefore, during the study the dose of irinotecan was reduced to 50mg/rn2. The efficacy of the combination of topotecan 1.25 mg/m2 per day days 1-5 and cisplatin 75 mg/m2 day 1 (arm A), and topotecan 1.0 mg/m2 per day days 1-5 and paclitaxel 190 mg/m2 day 1 (arm B), both with addition of G-CSF and administered once every 4 weeks, was evaluated in a randomized phase II study in. 83 patients with non-pretreated advanced non-small-cell lung cancer (149). Neither treatment arm showed activity (arm A response rate 14%, arm B 249/6) that can be considered superior to the activity of currently available regimens. Excessive toxicity was encountered for the combination of cisplatin

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TABLE 5 Phase II studies on combinations of irinotecan and topotecan in various tumour types

Tumour type Therapy scheme (mg(rn2 per day) No. of Response Reference
patients rate
(%)

First line

NSCLC CPT- 11 160 day I 41 54 146
CDDP 20 days 1-5+G-CSF
2pg/kg days 6-21 q.4weeks

CPT-II 60 days 1,8,15 52 31 147
CDDP day 80 day q. 4 weeks day I

CPT- 1160 days 1-3 61 21.3 148
16 60 days 3 + G-CSF 50 pg/rn2 per day
days 4-17 q. 3 weeks

Topotecan 1.25 days IS 22 14 149
CDDP 75 day I + G-CSF 5 pg/kg days 6-16
q. 4 weeks

Topotecan 1.0 days 1-5 61 24 149
Paclitaxel 190 day I + G-CSF 5 pg/kg days
6-16 q. 4 weeks

SCLC CPT. II 80 or 60 days I, 8, 15 75 78 150
CDDP 60 day I q. 4 weeks

Cervical cancer CPT- II 60 days I, 8, 15 30 68 153
CDDP 60 day I q. 4 weeks

Gastric cancer CPT- II 70 days I, IS 29 59 151
CDDP 80 day I q. 4 weeks

Second line

Gastric cancer CPT- II 70 days I, IS IS 27 151
CDDP 80 day I q. 4 weeks

Ovarian cancer CPT- 11 50 or 60 days 1,8,15 18 54 152
CDDP 50 or 60 day I q. 4 weeks

Clear cell cancer CPT- II 140 days I, IS 24 46 87
Mftomydn-C Lp. days I, IS q. 4 weeks

i.p., intraperitoneal: NSCLC, non-small-cell lung cancer, SCLC, small-cell lung cancer.

and topotecan; grade 4 neutropenia 62% and thrombocytopenia 76%,?grade 3 non-haemato-logical toxicity 43%. Neither regimen was re-commended for further study. Also, combination chemotherapy with the concurrent administration of irinotecan 60 mg/m2 per day days 1-3 and etoposide 60mg/rn2 per day days 1-3 every 3 weeks with G-CSF support revealed only modest efficacy against metastatic non-small-cell lung cancer in first-line therapy (response rate 21%, median duration of response 141 days, range 62-299 days) (148). The toxicity appeared manageable, and consisted of neu-tropenia (?- grade 3: 39%, complicated by infection in 15/24 patients), anaemia (?-_ grade 3: 8%), diar-rhoea (?t grade 3: 16%), elevation of transaminases and bilirubin (?_> grade 3: 59/6) and interstitial pneu-
moiiitis.

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Because predinical studies stressed the potential importance of sequential administration of topo-isomerase I inhibitors with various other classes of agents, further studies are required to determine the antitumour effect of these combinations.

CONCLUSION AND FUTURE

PERSPECTIVES

Topoisomerase I inhibitors are an important addition to the currently available classes of drugs. Relatively recently irinotecan was registered for use in cob - rectal cancer patients and topotecan for use in second-line chemotherapy for ovarian cancer. Ir-inotecan can be combined with antimetabolites and

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taxoids at relatively high doses. The doseintensity cancer are planned that will determine the con-
reached in combination with platin derivatives tribution of topotecan when used as part of front-
seems to depend on the administration schedule line combination therapy with, for example,
Iused.n sched es combining irinotecan with a paclitaxel and cisplatin.
single administration of CDDP, a higher dose in-
tensity could be achieved. Combinations of topo-
isomerase I and II inhibitors yielded much toxicity, REFERENCES
esieciallv mvelotoxicitv, mucositis and diarrhoea.
Even after addition of G-CSF the gain in dose in-
tensity was limited. However, growth factorsupport
seems to be warranted only ifthe antitumour activity
of a combination therapy is enhanced by achieving
a higher dose intensity. Furtherstudies are necessary
to evaluate the efficacy of these combination re-gimens. Combination therapy with topotecan re-gimeris. quired even more dose reductions than the single-agent dose. The reason for this particular difference
’ between topoisomerase I inhibitorsis not yet known. 7The sequence of drug administration in the com-binations influenced the severity of the observed side-effects. This might in part be explained by ’phaxmacokinetic interactions, by up-regulation of topoisomerase ll, by a change in cell cycle dis-tribution of the tumour and blood progenitor cells

and/or by the interaction between topoisomerase I inhibitor and DNA adducts. Clearly, all future trials

should be parallelled by pharmacokinetics studies in order to evaluate the existence of pharmacological interactions and sequence-dependent effects of a combination therapy. Further investigations are also needed to determine whether the more toxic se-

quences are the more cytotoxic. Because it is lessequences desirable to address this issue in phase ifi studies, it would be worthwhile to have these studies pre-

ceded by randomized phase II studies in ordereceded to exclude a major impact of drug sequences on anti-tumour activity.
In orderto reduce the side-effects and to maximize

the dose intensity of the combination therapy, other schemes of administration of the drugs should be evaluated, for example the administration once every 3 weeks of both CDDP and irinotecan, the reversed sequence of administration of topotecan in combination with CDDP, paditaxel, etoposide and doxorubicin, and schemes with different time in-tervals between the administration of the drugs. Considering the antitumour activity the com-bination of irinotecan and cisplatin in particular seems to be promising in patients with non-small-cell and small-cell lung cancer, gastric cancer and ovariançOptima1 utilization of irinotecan in ,ctnliiifion with-5-FU, with or without leucovorin, in patients with metastatic colorectal cancer will require further studies in chemonaive patients. The impact of irinotecan as adjuvant therapy has yet to
be explored.
Additional large studies in patients with ovarian

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HIM

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

2020

Bogota, D.C., Diciembre 14 de 2007

Abogado
ERNESTO CAVALIER FRANCO

ASUNTO Radicación 04-95472
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Evento

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Actuaciôn 430

Oficio 873 Folios

Patente de Invención fl Patente de Modelo de Utilidad

Via Nacional

Via PCT (fase nacional) Cap.[E Cap. II

No. Sol. Internacional PCT/JP02/10186.

Fecha de Presentación Internal. 26/03/2002.

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de Ia DecisiOn 486 de Ia ComisiOn de Ia Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 58 a 93 como se radicO inicialmente.
Folios: 58 a 93, el interesado solicita eliminar Ia
Frase "cantidad terapØuticamente aceptable" de Ia.
DescripciOn.

1.2. Reivindicaciones: I a 35 Folios 94 a 70 como se radicO inicialmente.
I a 4, Folios 170 a 171 modificado.
1.3 Prioridad: Folio: 01
26/03/2002, JP, 200284677.

1.4 Respuesta del solicitante Folios: 164 a 172.

2. Objeto de Ia invención

Titulo de Ia solicitud: USO DE DERIVADO DE INDOLOPIRROLOCARBAZOL Y OTRO AGENTE ANTICANCEROSO EN COMBINACION.

ReivindicaciOn 1: una preparaciOn combinada para administraciôn simultÆnea, separada o secuencial en el tratamiento del cancer, caracterizada porque comprende dos preparaciones separadas que son:

MA 16

a) Una preparación que comprende, en combinación con un vehiculo o diIuynte farmacØuticamente aceptable, un compuesto de formula IA:

o una sal farmacØuticamente aceptable del mismo; y

b) Una preparaciOn que comprende, en combinaciôn con un vehiculo o diluyente farmacØuticamente aceptable, por 10 menos un agente antitumoral seleccionado del grupo que consiste de: 5-fluorouracillo, doxorubicina, etoposido, cisplatin, carboplatin, irinotecan, topotecan y campotecina, o una sal farmacØuticamente aceptable de los mismos, en donde, si la preparaciOn contiene 5-fluorouracilo, puede contener ademÆs leucovorin o puedeestar combinada con una preparación separada de leucovorin.

El problema planteado en esta solicitud es la necesidad de proveer preparaciones combinadas para incrementar sinergIsticamente la actividad antitumoral.

Para solucionar este problema tØcnico la solicitud en estudio proporciona una preparaciOn que comprende: a) una composicion que contiene un compuesto de fOrmula IA, en combinaciOn con un vehiculo o diluyente farrnacØuticamente aceptable o una sal farmacØuticamente aceptable del mismo; y b) una preparaciOn que comprende, en combinación con un vehiculo 0 diluyente farmacØuticamente aceptable, por lo menos un agente antitumoral seleccionado del grupo que consiste de: 5-fluorouracilo, doxorubicina, etopOsido, cisplatin, carboplatin, irinotecan, topotecan y camptotecina, o una sal farmacØuticamente aceptable de los mismos, en donde si la preparación contiene 5-fluorouracilo, puede contener ademÆsleucovorin o puede estar combinada con una preparaciOn separada de leucovorin.

Una vez catalogada la invención esta se clasificO en la secciOn: A61 K31/7056, 31/4745,31/282,31/24,311704,3117048, 31/519,45/00, A61 P35/00,43/00.

3. De la solicitud de Patente

3.1. Reivindicaciones (artfculo 30 D 486)

ReivindicaciOn 1: En el preÆmbulo de estareivindicaciOn estÆn incluidas las formas de administración (mØtodo de tratamiento) las cuales se deben eliminar.

Son muchIsimas las combinaciones que se pueden obtener al mezclar a) y b) de la presente reivindicaciôn y no estÆn sustentadas, en ladescripciOn, para demostrar que las combinaciones de principios activos incrementen sinergIsticamente los efectos antitumorales.

Se sugiere limitar la reivindicaciOn a la combinaciOn que mostrO la sinergia, lo cual da soluciOn al problema objetivo de la solicitud.

MI

Reivindicación 4: Esta materia esta completamente comprendida en la reivindicaciôn I y no es claro porque no creó dependencia con esta.

4. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de la TØcnica es:

Fecha de presentaciOn de la solicitud prioritaria Marzo 26 de 2002.

Teniendo en cuenta la fecha indicada se realizó la büsqueda en el estado de la tØcnica de documentos relacionados con la solicitud encontrÆndose los siguientes documentos mÆsrelevantes:

No Documento Titulo Fecha de

publicación*

Dl US5922860 Antitumor Indolopyrrolocarbazole 1999-07-13 derivatives
The development of combination

D3 Articulo Clentifico therapy involving camptothecins: a 1998 review of preclinical and early clinical

studies*
* Cancer Treatment Reviews 1998; 24; 205-220.

5. AnÆlisis depatentabilidad (segün requisito) (artIculo 14 D486)

5.1 Novedad

La reivindicaciôn I y sus dependientes, se refieren a preparaciones separadas las cuales son:

a) PreparaciOn que comprende un compuesto de formula IA,

con un vehIculo o diluyente.
Teniendo en cuenta lo anterior, la novedad de la mencionada fOrmula se ye afectada por el documento Dl (folio 149 colum 2 renglon 30) que se refiere a compuestos derivados de Indolopirrolocarbazol con efecto antitumoral, representados por la formula general I:

b) Una preparaciôn que comprende, en combinación con un vehiculo o diluyente, por lo menos un agente antitumoral seleccionado de: 5-fluorouracilo, doxorubicina, etoposido, cisplatin, carboplatin, irinotecan, topotecan y camptotecina 0 una sal farmacØuticamente aceptable de los mismos, en donde si la preparación contiene 5-fluorouracilo pude contener ademÆsleucovorin o puede estar combinada con una preparaciOn separada de leucovorin.

Algunas de las modalidades de combinaciôn pueden ser: Irinotecan y topotecan; Irinotecan y Cisplatin; Cisplatin y Topotecan; Irinotecan y Carboplatin; Carboplatin y Topotecan; Etopôsido e Irinotecan; Topotecan y Etoposido; Doxorrubicina y CAmpotecina; Irinotecan y 5Fluorouracilo; Topotecan y 5Fluorouracilo; 5Fluorouracilo y LeucovorIn.

Teniendo en cuenta 10 anterior, la novedad de las mencionadas preparaciones se ye afectada por el documento D3 (folios 173-184) que se refiere al desarrollo de terapia de combinada con compuestos de camptotecina.

Con respecto a las preparaciones de b) de la presente reivindicación que no se yen afectados por novedad, a continuación se procederÆ a evaluar su nivel inventivo.

5.2 Nivel inventivo (artIculol8 D486)

La reivindicaciôn I b), se refiere a una preparacion que comprende, en combinación con un vehIculo o diluyente, por Jo menos un agente antitumoral seleccionado de: 5-fluorouracilo, doxorubicina, etoposido, cisplatin, carboplatin, irinotecan, topotecan y camptotecina o una sal farmacØuticamente aceptable de los mismos, en donde si la preparaciOn contiene 5-fluorouracilo pude contener ademÆs leucovorin o puede estar combinada con una preparación separada de leucovorin.

Dicha preparación esta afectada en su nivel inventivo por el siguiente documento mÆscercano encontrado en el Estado de la TØcnica:

D3 que se refiere al desarrollo de terapia de combinada con compuestos de camptotecina.

La diferencia de la solicitud con D3 es que, pretende reivindicar otra gran cantidad de preparaciones combinando los activos mencionados anteriormente: 5-fluorouracilo, doxorubicina, etôposido, cisplatin, carboplatin, irinotecan, topotecan y camptotecina o una sal farmacØuticamente aceptable de los mismos, en donde si la preparaciôn contiene 5-fluorouracilo pude contener ademÆs leucovorin o puede estar combinada con una preparación separada de leucovorin, pero eStas combinaciones no parecen conceder un efecto tØcnico inesperado porque estos siguen siendo para tratar el cancer.

El problema planteado en esta solicitud es la necesidad de proveer preparaciones combinadas para incrementar sinergIsticamente la actividad antitumoral, se habla resuelto previamente mediänte combinaciones de antitumorales ya conocidos.

Por esta razón se considera que las combinaciones reivindicadas son evidentes para una persona medianamente versada en la materia.

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Adicionalmente en la descripción no se allegan ensayos experimentales (dato y resultados) realizados con todas las combinaciones que se pretende proteger de. acuerdo a la reivindicación 1, que sustenten:

1- Sinergia (relación de duraciôn de vida incrementada, ILS%) con las dosis a las cuales se muestra la mencionada sinergia.
2- Una velocidad de inhibiciôn de crecimiento del tumor, %.
3- Cambio de peso corporal, en gramos.

En los cuadros 3y 4, solo se allegan resultados para la mezcla de: compuesto A (0.3mg/Kg) + Leucovorin (83.3mg/Kg) + 5 fLuorouracilo (10mg/Kg), que comparada con:

1- El compuesto A cuando se aplica solo,
2- Con la mezcla de Leucovorin (83.3mg/Kg) + 5 fLuorouracilo (10mg/Kg); muestra un efecto de la velocidad de inhibición del tumor mayor (30%).

En los cuadros 5y 6, solo se compara: el compuesto A (25mg/Kg) y la Adriamicina (doxorubicina, 1.5mg) solos, contra la combinaciôn de compuesto A (5mg/Kg) + Adriamicina (doxorubicina 0.3mg/Kg), observÆndose gue el tiempo de vida disminuve con la combinaciôn a 83 dias, comparado con el tiempo de 93 dIas al administrar solo la ADM.

El anÆlisis anterior muestra que solo se tiene un resultado conactividad de sinergia para la mezcla de: compuesto A (0.3mg/Kg) + Leucovorin (83.3mg/Kg) + 5 fLuorouracilo (10mg/Kg), en las condiciones en las que se realizo el ensayo (pg 32,folio 90), pero no hay sustento respecto a Ia duraciOn de vida incrementada y el cambio de peso corporal, adicionalmente este resultado no es extrapolable para todas las otras combinaciones que se pretende proteger.

AdemÆs, ya que D3 (173-184) divulgaba previamente combinaciones que mostraron sinergia con actividad antitumoral, una persona conocedora de la materia motivada portal sugerencia lograrla las dichas preparaciones, combinando los compuestos o principios cativos mencionados en esta reivindicaciôn, que presentan actividad antitumoral. Par Ia cual no tienen Nivel Inventivo.

La reivindicaciôn 4, se refiere a: Una composiciôn farmacØutica, caracterizada porque comprende, en combinación con un vehIculo o diluyente farmacØuticamente aceptable:

a) Un compuesto de formula IA:

una sal farmacØuticamente aceptable del mismo; y b) par Ia menos un agente antitumoral seleccionado del grupo que consiste: 5-fluorouracilo, doxorubicina, etOposido, cisplatin, carboplatin, irinotecan, topotecan y camptotecina a una sal

farmacØuticamente aceptable de los mismos, en donde si la preparación contien1e - fluorouracilo pude contener ademÆsleucovorIn o puede estar combinada con una

preparaciOn separada de leucovorin.

El documento del Estado de la TØcnica mÆs próximo es D3 que enseæa preparaciones combinando compuestos con actividad antitumoral (Ver folios: 173-

184), la 6nica diferencia con D3 es que esta solicitud menciona en la composiciOn farmacØutica de dicha reivindicación el compuesto de fOrmula IA, pero esto no parece conceder un efecto tØcnico inesperado porque esta composiciOn sigue conservando la actividad antitumoral.

El problema planteado en esta solicitud que es (a necesidad de proveer preparaciones combinadas para incrementar sinergIsticamente (a actividad

antitumoral, se habia resuelto previamente mediante combinaciones de antitumorales ya conocidos.

Por esta razón se considera que las combinaciones reivindicadas son evidentes para una persona medianamente versada en la materia.

Adicionalmente se reitera que el anÆlisisde los cuadros 3,4,5 y 6 allegados en (a descripciOn solo se tiene un resultado con actividad de sinergia para la mezcla de:
compuesto A (0.3mg/Kg) + Leucovorin (83.3mg/Kg) + 5 fLuorouracilo (10mg/Kg), en las condiciones en las que se realizo el ensayo (pg 32,folio 90), pero no hay sustento respecto a la duración de vida incrementada y el cambio de peso corporal, adicionalmente este resultado no es extrapolable para todas las otras combinaciones que se pretende proteger.

AdemÆs, dado que DI (folios 148-151) divulgaba compuestos de formula IA con actividad antitumoral y D3 (173-184) divulgaba previamente combinaciones que mostraron sinergia con actividad antitumoral, una persona conocedora de Pa materia motivada por tal sugerencia lograrla (a composiciOn de esta reivindicaciOn, que presenta una actividad antitumoral, combinando estos dos documentos. Por lo cual no tiene Nivel Inventivo.

6. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados as!:

N° Documento N° Reivindicaciones

afectadas Requisito que afecta

Dl US5922860 I a) Novedad ReivindicaciOn 4 Nivel Inventivo
Novedad Nivel

D3 Articulo Cientifico I b) Inventivo
Nivel Inventivo Reivindicaci6n_4 1

14 Respuesta a los argumentos del solicitante:

Dado que el interesado decidiO limitar el compuesto A, a un compuesto de fOrmula IA, se solicita que allegue el nombre IUPAC del mismo.

- Una vez tenida en cuenta esta observación y las hechas en los numerales 3.1 y.2, se debe incluir en el tItulo los nombres de los compuestos que conforman la mezcla para la que se demuestro la actividad sinergistica. Lo anterior con el fin de que el nuevo tItulo divulgue de manera suficiente, clara y completa la materia comprendida en la invención.

En cumplimiento del articulo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dIas contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, 0 si a pesar de la respuesta subsistieran los impedimentos para la concesiOn, se denegara la patente.

Notifiquese el presente oficio cpnföThe a lo dispuesto en el numeral 5.2, literal e), del capItulo quinto del titilo prpiØro de 14 Circular Unica NO 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de Divisk’n de Nuevas Creaciones

anterior &El requerimiento fue notificado por fijaciOn en lista, de fecha

2 Ef:. 2R

CONCEPTO TECNICO
No. 2583

EXAMINADOR TECNICO
Codigo No. 202078