

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-671/S-004

MEDICAL REVIEW(S)

MEDICAL REVIEW OF NDA 20-671: Hycamtin® (Topotecan)

Supplement for New Indication: Small Cell Lung Cancer

SPONSOR: SmithKline Beecham

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ODAC MEETING: June, 2, 1998

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1.0 General Information

Drug name: Hycamtin (topotecan)

Applicant: SmithKline Beecham

Supplemental NDA Submission Date: December 5, 1997

Pharmacologic Category: Topoisomerase I inhibitor

Proposed Indication: Second line therapy for small cell lung cancer

Safety Update: to follow

Advisory Committee Meeting: June 2, 1998

Materials Used for Review: Volumes 11, 12, 13, 32, 42, 52, 64, 71, 72, 73, and 74 of the original submission

Electronic Dataset on CD-ROM

Updated datasets submitted electronically or by fax on January 16, 1998, April 28, May 1, May 4, and May 8, 1998

2.0 Abstract and Background

NDA application 20-671 presents data on 211 patients with sensitive small cell lung cancer (SCLC) in a Phase III randomized comparative study, and data on an additional 319 patients with either sensitive or refractory SCLC in 3 Phase II supportive studies where the entry criteria, treatment, and assessment were similar to that for the pivotal study.

Small cell lung cancer is diagnosed in greater than 40 000 patients annually in North America. It is characterized by the proliferation of cells of neuroendocrine origin within the lung tissue. There are several chromosomal abnormalities that are associated with, but not diagnostic of lung cancer. Without therapy median survival is in the range of 2 to 4 months with a 5 year survival of less than 1%. With the use of systemic chemotherapy, median survival is usually greater than 12 months and 5-year survival is between 5 and 10%. On a cellular level, there is decreased expression of Type I major histocompatibility antigens and increased expression of a variety of hormonal secretory products. The presence of greater than normal levels of hormonal products can lead to a variety of clinical endocrine abnormalities that result in paraneoplastic phenomena.

Small cell lung cancer is described as limited if only parenchymal lung tissue is involved, otherwise any extra-pulmonary involvement is termed extensive disease. The response to an initial chemotherapy regimen is generally good, leading to general optimism that cytotoxic chemotherapy can be an important component of treatment. Unfortunately, most tumors recur within a relatively short period of time, and are less amenable to treatment. Tumor that recurs within 3 months of the initial regimen is considered refractory, while tumor that occurs later than 3 months is considered sensitive.

Active agents in current use include etoposide, cyclophosphamide, ifosfamide, doxorubicin, methotrexate, vincristine, cisplatin and carboplatin. Most regimens consist of a combination of either cisplatin with etoposide (CE) or cyclophosphamide, doxorubicin, and vincristine (CAV). Four to six cycles has been shown to be an optimal number with shorter courses compromising the response and longer courses only adding toxicity. There have not been any survival advantages demonstrated comparing CE to CAV. Some regimens alternate CE with CAV, but again there is no survival advantage. For patients with limited disease there are small statistical advantages in survival based on meta-analysis in receiving combined modality therapy of chemotherapy plus radiation.

Second line therapy is usually combination chemotherapy with either the initial regimen if the patient is considered sensitive or with another

regimen if the patient is considered refractory or resistant. Response rates are never as high as initially, and the therapeutic goal is usually palliation and improved quality of life.

The Phase III study compared a regimen of topotecan monotherapy given at a dose of 1.5 mg/m² as a 30 minute intravenous infusion for 5 consecutive days on a 21 day cycle with a regimen of cyclophosphamide 1 gram/m² IV plus doxorubicin 45 mg/m² IV plus vincristine 2 mg IV all given on day 1 of a 21 day cycle. The results were that the response rates, median duration of response, time to progression and median survival were similar in each arm. For disease related symptoms, there was greater improvement for 1/5 to 1/3 of the patients in 8 of 9 symptoms measured for the topotecan arm compared to the control arm. Limitations on the methodology preclude formal statistical comparison.

The data in the other 3 trials were consistent with response rates ranging from 11 to 31 %, median duration of response approximately 20 weeks in all studies, time to progression ranged from 10 to 17 weeks for sensitive patients and from 6 to 21 weeks for refractory patients, and median survival ranged from 26 to 35 weeks for sensitive patients and 16 to 21 weeks for refractory patients.

Toxicities were primarily hematologic with Grade 4 neutropenia occurring in almost 75% of patients and almost 40% of courses. Leukopenia was recorded in about 31% of patients and 12% of courses, thrombocytopenia in 28% of patients and 11% of courses, and anemia in 33% of patients and 13% of courses.

Therapy related complications included the need for red blood cell transfusions which were administered in 23% of courses, and platelet transfusions in almost 6% of courses. Febrile neutropenia or sepsis occurred in almost 17% of patients and 6% of courses. Deaths associated with topotecan treatment occurred in about 3% of patients.

Non-hematologic toxicities were primarily gastrointestinal. Almost 49% of patients had nausea, 32% emesis, 20% diarrhea and 19% constipation. Serious adverse events (Grade 3 or 4) were limited to 5% of patients with Grade 3 nausea and 2.6% with Grade 3 emesis. Other non-hematologic toxicities that occurred in over 10% of patients included asthenia in 29%, dyspnea in 25%, alopecia in 39%, pain in 22.5%, headache in 13.8 %, fever in 21.1 %, fatigue in 20%, and cough in 18.5%.

Treatment-related deaths occurred in about 3% of patients with small cell lung cancer.

The toxicity profile was similar to that described for other clinical trials conducted with topotecan in ovarian cancer, and indeed a composite analysis confirms these findings.

To summarize, topotecan demonstrated antitumor activity and some evidence of patient benefit in patients with small cell lung cancer that did not respond to or recurred following first line treatment. The toxicities were not different from those anticipated from current labeling for topotecan with the most frequent and severe being hematologic toxicities which can lead in some cases to fatal complications. The current label contains a boxed warning to this effect.

The patient population appears to be appropriate for the indication and the trials present a variety of comparators. In all of the trials, response criteria were defined and appear to have been based on objective measures such as bidimensional tumor measurements.

**APPEARS THIS WAY
ON ORIGINAL**

3.0 Scope of Review

This review is for a supplemental application of an approved drug that has not had a measurable incidence of unanticipated adverse events based on a survey of the Medwatch and Spontaneous Reporting Databases at the FDA as of March 1998. The review will focus, therefore, on the new information related to the new claimed indication, and refer to the current label and previous material for further background information related to the chemistry, pharmacology, toxicology, pharmacokinetics and other clinical data.

4.0 Regulatory History

Related IND Submissions

The first IND for topotecan was submitted on March 2, 1989, with subsequent INDs being filed on March 28, 1990 and August 18, 1993 for an oral formulation.

An end of Phase II meeting occurred on May 11, 1993 for the development of a pivotal study for ovarian cancer. A pre-NDA meeting occurred on September 8, 1995, and the NDA was filed on December 21, 1995. It was presented before an advisory committee on April 19, 1996, which recommended approval, and was approved with the trade name *Hycamtin* on May 28, 1996, 159 days following submission.

The current supplement was filed on December 5, 1997.

Foreign Marketing

Approval in the European Union occurred on November 12, 1996. *Hycamtin* has not been refused marketing authorization in any country on safety grounds, nor been withdrawn from marketing in any country.

5.0 Chemistry and Manufacturing

See previous submissions and chemistry review for details

6.0 Preclinical Pharmacology and Toxicology

See previous submissions and chemistry review for details

7.0 Clinical Pharmacology and Pharmacokinetics

See previous submissions and chemistry review for details. In brief, topotecan is administered intravenously as a 30 minute infusion in normal saline. Like camptothecin, topotecan has a lactone ring that can be reversibly hydrolyzed depending upon pH. The lactone structure is favored in an acid environment. At neutral or physiologic pH the inactive hydroxy acid form is favored.

Following infusion, topotecan is widely distributed in a high volume of distribution about 3 times that of total body water. Binding to plasma proteins is less than 35%, with a blood to plasma distribution ratio of 1.2:1.

Clearance is primarily renal with an indeterminate eliminated through feces. There is hepatic conversion of some fraction of the topotecan to an N-demethylated metabolite, which appears as about 2.5% of the urine excreted dose. Technical difficulties in measuring topotecan in acidified urine led to a wide range of estimates of the dose fraction that is excreted, from 20 to 60%.

There is plasma clearance of 62 L/h, which when combined with the high volume of distribution, results in an estimated half life of 2 to 3 hours. There is no measurable change that occurs with repeated dosing over a 5 day course. The AUC is proportional to the dose.

In patients with hepatic impairment, the clearance was 2/3 of normal and half life was increased about 1/3. Similar observations are seen in patients with mild (creatinine clearance of 41-40 ml/min) renal impairment. Patients with moderate renal impairment (creatinine clearance 20-40 ml/min) had a clearance which was only 1/3 of normal, a decrease in the volume of distribution by 25%, and an increase in the plasma half life to almost 5 hours.

There is a measurable gender difference in clearance with male patients having about a 24% higher value than female patients.

In patients with small cell lung cancer receiving a dose of 2 mg/m² daily for 5 days, population pharmacokinetics for total topotecan (lactone +hydroxy acid) showed similar or slightly higher clearance values compared to Phase I studies. Body weight correlated with peripheral volume of distribution and creatinine clearance correlated with total topotecan clearance. The values differed from population studied for ovarian cancer possible due to two factors, the previous chemotherapy regimen and the fact that all ovarian patients were women.

There was a correlation between total topotecan area under the curve and Grade 3 and 4 leukopenia in a 24 hour infusion study in Phase I patients. This correlated with topotecan (lactone form) concentrations, which is

consistent with being able to measure either parameter to gauge exposure and relate it to toxicity.

8.0 Pivotal Clinical Study

8.1 Name and Dates

The name of the pivotal study is "Study 090- An open label multicenter randomized Phase III study of topotecan as single agent second line therapy administered intravenously as five daily doses every 21 days versus second line CV in patients with SCLC who have relapsed at least sixty day after completion of first line therapy." First patient enrollment was June 19, 1995. Last patient enrolled was March 6, 1997. Data collection ended on May 30, 1997.

8.2 Design

The following section was modified from the original protocol text provided by the sponsor.

Trial 090 was an open, multicenter, comparative study to evaluate the efficacy and toxicity of topotecan for the treatment of patients with small cell lung cancer who have relapsed at least sixty days after first-line chemotherapy. Eligible patients with bidimensionally measurable disease were randomized for treatment either with topotecan administered as five daily 30-minute infusions every 21 days, or with the combination of cyclophosphamide, doxorubicin and vincristine (CAV) administered once every 21 days. Therapy was planned for a minimum of six courses.

Clinical and laboratory parameters were assessed to evaluate disease response, survival, and the qualitative and quantitative toxicities of topotecan and of CAV administered on these schedules.

The pharmacokinetics of topotecan was assessed, using population techniques as the data permitted.

Primary Objectives

- To evaluate the response rate and response duration in relapsed patients with limited or extensive small cell lung cancer, following treatment with single agent topotecan administered as five daily 30-minute infusions every 21 days, or with a combination of

cyclophosphamide, doxorubicin and vincristine (CAV) administered once every 21 days.

Secondary Objectives

- To evaluate the time to response, time to progression, survival and symptoms of disease in relapsed patients with local or extensive SCLC treated with topotecan or with CAV administered on these schedules.
- To evaluate the qualitative and quantitative toxicities of topotecan and of CAV administered on these schedules.
- To evaluate the pharmacokinetics of topotecan administered as a 30 minute infusion for five consecutive days every 21 days.

Inclusion Criteria

- Written informed consent
- Age at least 18 years old.
- Documented progressive or recurrent, limited or extensive, SCLC.
- One and no more than one prior regimen of first-line chemotherapy.
- Documented partial response or complete response to first-line therapy.
- Date of first documentation of a patient's recurrence of small cell lung cancer must be at least 60 days after the date of his/her last treatment of first-line chemotherapy.
- At least one bidimensionally measurable, non-CNS lesion, defined by diagnostic studies including CT or MRI scan, ultrasound or chest X-ray. Cytologic or histologic proof of malignancy is required in the case of a single lesion including liver, skin, or accessible lymph node. It is strongly preferred that every lesion be measured by CT or MRI scan, radiograph, ultrasound, or photograph; however tumor measurements may be made by physical examination. A scale must be noted on all CT or MRI scans, ultrasounds, and photographs that will be used to evaluate lesions. The same diagnostic method must be used throughout the study to evaluate response or progression of the lesions.

- Measurable disease on CT or MRI scan, or ultrasound **must** have at least one diameter ≥ 1 cm. Indicator Lesions measured only by chest x-ray must have at least one diameter ≥ 2 cm.
- A measurable skin lesion must have at least one diameter ≥ 1.0 cm and its presence must be verified by a photograph.
- At least 4 weeks since last surgery (a lesser period is acceptable if deemed in the best interest of the patient).
- At least 24 hours since last radiotherapy treatment. The measurable indicator lesion(s) may be in the field(s) of prior radiation if at least 6 weeks have elapsed since the last radiotherapy treatment.
- At least 4 weeks since last immunotherapy treatment.
- At least 60 days since last chemotherapy.
- Current laboratory values must be within the limits listed below:
 - hemoglobin ≥ 9.0 g/dL (after transfusion if needed)
 - WBC $\geq 3,500/\text{mm}^3$
 - neutrophils $\geq 1,500/\text{mm}^3$
 - platelets $\geq 100,000/\text{mm}^3$
 - creatinine ≤ 1.5 mg/dL (133 $\mu\text{mol/l}$) or creatinine clearance ≥ 60 ml/min
 - serum bilirubin ≤ 2.0 mg/dL (34 $\mu\text{mol/l}$)
 - SGOT/AST, SGPT/ALT, and Alkaline Phosphatase ≤ 2 times the upper limit of normal if no liver metastases by abdominal CT or MRI, or ≤ 3 times the upper limit of normal if liver metastases present.
- Performance status ≤ 2 (Appendix E); and life expectancy ≥ 3 months.

Exclusion Criteria

- More than one previous regimen of chemotherapy.

- Progressive or recurrent small cell lung cancer documented to have recurred **less** than 60 days following completion of first-line chemotherapy.
- Absence of at least one bidimensionally measurable indicator lesion.
- Present clinical signs or symptoms of brain and/or leptomeningeal metastases confirmed by CT or MRI brain scan. A patient with brain and/or leptomeningeal metastases on CT or MRI scan may be included only if he/she is asymptomatic on neurologic exam and is not receiving corticosteroid therapy to control symptoms.
- Concomitant malignancies or previous malignancies other than SCLC within the last five years, excepting basal and squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix.
- Active uncontrolled infection.
- Concurrent severe medical problems unrelated to the malignancy which would significantly limit full compliance with the study or expose the patient to extreme risk decreased life expectancy.
- Treatment with an investigational drug within 30 days or five half-lives prior to entry into the study, whichever is longer.
- Concurrent other chemotherapy, immunotherapy, radiotherapy, or investigational therapy for the treatment of small cell lung cancer.
- Prior treatment with topotecan or camptothecin analogue.
- History of allergic reactions to compounds chemically related to topotecan or to cyclophosphamide, doxorubicin or vincristine.
- Pre-existing cardiac disease, including clinical congestive heart failure, arrhythmias requiring treatment, or a myocardial infarction within the preceding three months.
- Any other medical condition for which treatment with CAV is contraindicated, including a demyelinating polyneuropathy, or poliomyelitis.
- A total lifetime cumulative dose of doxorubicin exceeding 270 mg/m² or cumulative dose of epirubicin exceeding 540 mg/m².
- Being of reproductive potential and not agreeing to practice an effective contraceptive method. Examples include: for females, oral contraceptives or IUD for 3 months prior to the start of the study

medication or diaphragm plus spermicide; and for males: condom plus spermicide.

- Pregnancy or lactation.

Screening Evaluation

The following parameters were assessed **within 14 days** prior to first scheduled treatment in order to determine eligibility for entry into the study:

- Complete medical history including details of malignancy, documentation of histology, prior treatment(s) including response and any residual toxicity related to prior therapies.
- Assessment of nine symptoms of disease by patient's answers to questionnaire provided as Case Report Form
- Performance Status: ECOG Scale (Appendix E).
- Physical exam including vital signs (blood pressure and pulse rate after 5 minutes sitting, body temperature), body weight and height.
- Neurologic Exam.
- 12-lead ECG.
- Chest X-ray.
- Chest CT Scan or MRI Scan.
- Abdominal CT or MRI Scan or Ultrasound.

The following parameters were assessed **within 28 days** prior to first treatment:

- Echocardiographic or Radionuclide Ventriculographic measure of left ventricular ejection fraction (LVEF).
- Radionuclide bone scan.
- Brain CT or MRI Scan.

Laboratory Evaluation must be performed prior to the first treatment with either topotecan or CAV. Before the first treatment, all results must be within the limits listed in the inclusion criteria.

For all trial sites in North America, blood chemistry, urinalysis and serum beta-HCG pregnancy tests were performed by a central laboratory facility

Hematology evaluation was schedule **within 7 days** of first treatment and repeated if any abnormal value was clinically significant.

- CBC with WBC, Differential, Platelets

Blood Chemistry, Pregnancy Test (if appropriate), and Urinalysis were scheduled **within 14 days** of first treatment and repeated if any abnormal value is clinically significant.

- Sodium, Potassium, Chloride, Bicarbonate, Calcium, Phosphorus, Magnesium, BUN or Urea, Uric Acid,

Creatinine (Creatinine Clearance if Creatinine is ≥ 1.5 g/dL),

Alkaline Phosphatase,

SGOT/AST, SGPT/ALT,

Total Bilirubin, Direct Bilirubin,

Total Protein, Albumin.

- Serum Beta-HCG Pregnancy Test

Women of child-bearing potential were **required** to have a serum Beta-HCG pregnancy test. (Child-bearing potential is defined as women who are not surgically sterilized or post-menopausal; i.e., documented absence of menses for one year prior to entry into the study.)

- Dipstick Urinalysis

Microscopic examination **required** if Dipstick is positive for blood or protein.

- Any other diagnostic studies required for complete tumor assessment.
- Documentation of tumor status at time of entry including **all** measurable and evaluable disease with identification of **at least one indicator lesion** to be used for assessment of response.

- **Indicator lesions must meet criteria for measurable disease and must be assessed using CT or MRI scan, ultrasound, x-ray or photograph.**
- Documentation of indicator lesion(s) to include date of assessment, description of lesion site, dimensions, and type of diagnostic study used to follow lesion. The same diagnostic method **must** be used throughout the study to evaluate a lesion.

8.3 Treatment Plan

Eligible patients were randomized to receive either:

topotecan 1.5 mg/m²/day as a 30-minute intravenous infusion for 5 consecutive days, every 21 days;

- or -

an intravenous chemotherapy regimen of cyclophosphamide 1000 mg/m² + doxorubicin (Adriamycin®) 45 mg/m² + vincristine 2 mg, administered sequentially on day 1, every 21 days.

Vital signs (blood pressure, pulse rate, and body temperature) were taken prior to treatment (0 minutes) and prior to discharge.

- On discharge, investigators will give information to the patient outlining signs and symptoms suggesting possible infection; and investigators will instruct each patient to notify the investigator or study coordinator if their (the patient's) oral temperature is $\geq 38.1^{\circ}\text{C}$ or 100.5°F .
- Prophylactic or therapeutic anti-emetic therapy was given at the investigators' discretion.

Procedure For Dose Modifications