

A Mathematical Skew-Logistic Model for G-Flip is An Effective Treatment for Chemotherapy Refractory Metastatic Pancreatic Cancer

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Abstract: *In this paper we introduce the skew logistic distribution. It is observed that the probability density function of the skew logistic distribution is always unimodal. In this paper, we mainly consider the generalization of the logistic distribution by introducing skewness parameters. The main idea is to introduce the skewness parameter, so that the generalized logistic distribution can be used to model data exhibiting a unimodal density function having some skewness present in the data, a feature which is very common in practice. Patients with Single agents have only modest activity as treatment for metastatic pancreatic cancer with response rates of less than 10% and median survivals of less than 6 months. Evaluations of single-agent gemcitabine and rubececan as second-line treatment for relapsed pancreatic cancer have reported good patient tolerability and median survivals of 3.85 months and 4.7 months respectively. Adding a single new drug such as irinotecan to the same first-line chemotherapy combination upon disease progression may be an important alternative to switching to different drug classes for treatment of relapsed/resistant cancer. The outcomes and moderate toxicity associated with G-FLIP in this heavily pretreated group warrant development of this regimen including tests as first-line therapy in patients with diseases likely to be responsive to the drugs contained in this combination. The combination of G-FLIP is a generally well-tolerated and effective regimen that provided sustained disease control in intensively metastatic pancreatic cancer patients. Our mathematical results shows G-FLIP drugs combinations are well tolerated treatment option. The medical curve and mathematical curve for disease control is higher than the probability density functions which are monotonically increasing function.*

Keywords: Gemcitabine, Irinotecan, 5-fluorouracil, leucovorin, cisplatin, skew logistic distribution.

Mathematical subject classification: 60 G₁₂, 62 H₁₂, 62 P₁₆.

1. Introduction

Approximately 30,000 cases of adenocarcinoma of the exocrine pancreas are diagnosed. The majority of these tumors are unresectable and resistant to systematic therapy. Response rates of less than 10% and median survival times of less than 6 months are associated with single-agent chemotherapy. Gemcitabine produced a response rate in 24% of patients, with a median survival of 5.6 months and 1-year survival of 18% [2]. Alternative single agents have been investigated in patients with metastatic pancreatic cancer. Irinotecan (CPT-11, Camptosar) is well tolerated and associated with response rates of close to 10% in both weekly and once every 3 week schedules. The feasibility and efficacy of most conceivable doublet combinations of gemcitabine, irinotecan, cisplatin and 5-fluorouracil (5-FU) have been demonstrated in patients with metastatic pancreatic cancer. Response rates of 12% to 30% and median survivals of 8 or more months have been attained with gemcitabine/cisplatin combinations. Gemcitabine/5-FU and 5-FU/cisplatin have been associated with CBRs ranging from 50% to 60%, stable disease (SD) and partial response (PR) rates varying from 20% to 65%, TTP ranging from 12 to 30 weeks and median survivals of upto 11 months [3, 7, 9, 11]. Options for patients with relapsed pancreatic cancer are of limited benefit. Evaluations of single-agent gemcitabine or rubececan salvage therapies for metastatic pancreatic cancer have reported good patient tolerability but median survivals of only 3.85 and 4.7 months respectively [12].

Based on the reported interaction among all of these drugs given as doublets, we hypothesized that a four-drug combination of gemcitabine, 5-FU/leucovorin, cisplatin and irinotecan (G-FLIP) would be an effective salvage regimen for patients whose disease had progressed on gemcitabine-based regimens. Favorable drug interactions were demonstrated between gemcitabine coupled with either cisplatin, irinotecan or 5-FU. The G-FLIP regimen was designed to approximate sequence-dependent synergistic or additive interactions while attempting to minimize sequence-dependent toxic effects among the four drugs. This retrospective analysis examined the outcome of 34 consecutive patients treated with G-FLIP. All patients had histologically confirmed metastatic adenocarcinoma of the exocrine pancreas. Patients were assessed with weekly CBCs, liver function profiles, serum electrolytes, and serum creatinine while receiving treatment. Day 1 treatment consisted of sequentially administered gemcitabine 500 mg/m², irinotecan 80 mg/m², and then leucovorin 300 mg, 5-FU 400 mg/m² bolus followed by infusional 5-FU 600 mg/m² over 8 hours. Day 2 treatment consisted of leucovorin 300 mg and 5-FU 400 mg/m² bolus followed by cisplatin 50 to 75 mg/m², and then infusional 5-FU 600 mg/m² over 8 hours. All other patients received cisplatin 75 mg/m². Treatment was repeated every 14 days. Kytril 2 mg orally and decadron 10 mg were given as antiemetic prophylaxis 30 minutes prior to chemotherapy on days 1 and 2. Intravenous normal saline at 200 cc/hour for 4 hours with lasix 10 mg i.v. was given to ensure a urine output of at least 100 cc/hour prior to cisplatin administration. Normal saline

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hydration was continued for 6 hours at 125 cc/hour after the completion of cisplatin. Patients were evaluated weekly for nonhematological toxicity and once or twice weekly for hematological toxicity. In particular, renal toxicity, vomiting, and neutrotoxicity prompted modification of 5-FU dosages.

2. Application

The median patient age was 64.5 years (range: 41-82) and 25 patients were men. All patients had metastatic disease with at least one lesion measurable by CT. Most patients had extensive metastatic spread: 26 patients had liver metastases, five had lung metastases, five had peritoneal metastases, and 15 patients had more than one site of metastatic disease. A total of 476 cycles of G-FLIP were administered. The median number of cycles per patient was five (range: 1-25). The median dose intensities for each drug expressed as mg/m²/2 weeks were as follows: gemcitabine 433, irinotecan 60, 5-FU bolus 600, 5-FU infusion 1,200 and cisplatin 36. Grade 3-4 toxicities per patient included thrombocytopenia (53%), neutropenia (38%) and anemia (23%). These toxicities were easily managed and there were no grade 3-4 neutropenic fevers or hemorrhagic events. Grade 3-4 nonhematological toxic side effects were rare. Grade 3-4 pares thesias occurred in 3% of patients. nephrotoxicity occurred more frequently and included vomiting (47%), diarrhea (18%), mucositis (12%), paresthesias (24%) and nephrotoxicity (12%). Eight patients attained a PR, seven patients had disease stabilization and 19 had disease progression. The median TTP for all 34 patients was 3.9 months. TTP for the eight patients who attained a PR was 5.9 months. Median overall survival measured from the start of G-FLIP was 10.3 months. Thirty-one patients received G-FLIP after demonstrated disease progression on GFP. In this sequentially treated group there were seven patients who each attained either a PR or stable disease. Median TTPs were 2.3 months for all 31 patients and 5.8 months for the seven patients who attained a PR. Measured from the initiation of GFP, the median survival for the 31 sequentially treated patients was 11.8 months, 1-year survival was 47%, and 2-year survival was 24%. Eight of the 14 patients who attained as PR or SD with G-FLIP had disease progression as a best response to prior GFP in the figure 2.1.

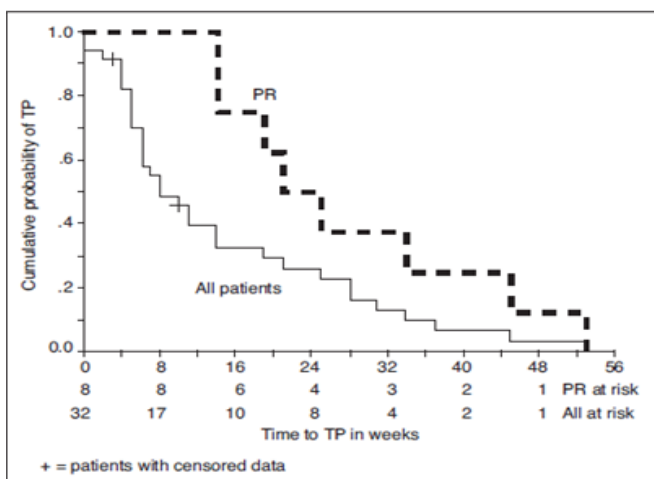


Figure 2.1: TTP for all patients and for patients with PR

3. Mathematical Model

The random variable X has the logistic distribution if it has the following cumulative distribution function

$$F(x; \mu, \sigma) = \frac{1}{1 + e^{-\frac{x-\mu}{\sigma}}}, \quad -\infty < x < \infty \text{-----(1)}$$

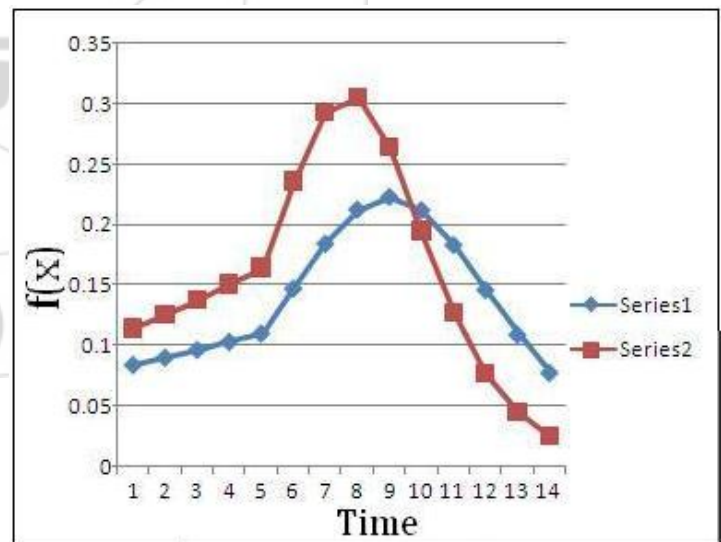
For any arbitrary location parameter μ and for the scale parameter $\sigma > 0$. The probability density function corresponding to the equation (1) is

$$f(x; \mu, \sigma) = \frac{e^{-\frac{x-\mu}{\sigma}}}{\sigma \left(1 + e^{-\frac{x-\mu}{\sigma}}\right)^2}, \quad -\infty < x < \infty \text{-----(2)}$$

Clearly, the probability density function given in (2) is symmetric about the location parameter μ . From now on the logistic distribution with the probability density function given in (2) will be denoted as $L(\mu, \sigma)$.

It is observed that the PDF of the skew logistic distribution can have different shapes with both positive and negative skewness depending on the skewness parameter. Although the PDF of the skew logistic distribution is unimodal. Moreover, it is observed that even when the location and scale parameters are known, the maximum likelihood estimator of the skewness parameter may not always exist.

4. Mathematical Results



5. Discussion

Gemcitabine is the first drug to approved for the treatment of pancreatic cancer. Gemcitabine-based doublets with 5-FU, cisplatin and irinotecan are feasible and there is a consistent suggestion of improved response rates, response duration, overall survival, and quality of life compared with contemporary reports of gemcitabine alone [3,7,9,10,11]. Single-agent second-line therapy for metastatic pancreatic cancer following gemcitabine failure has been associated with a median survival of less than 5 months [13]. The 1- and

2-year survival outcomes associated with the sequential use of GFP and G-FLIP compare favourably with both single-agent and combination therapies. The tolerability and efficacy of the G-FLIP regimen may in part be due to the rational sequencing of the drugs. G-FLIP was designed to approximate the known schedule dependent synergistic relationships among the four drugs and to minimize sequence-dependent toxic effects. Irinotecan was administered prior to 5-FU in the G-FLIP regimen. Furthermore, the sequence of 5-FU following irinotecan has been associated with less diarrhea and neutropenia. Pharmacodynamics, kinetics, and toxic side effects were not affected by the sequence of irinotecan-cisplatin administration [4,5]. Pharmacokinetic (PK) studies have not demonstrated a difference between sequences of gemcitabine and cisplatin when the two drugs are given 4 hours apart. However, gemcitabine 24 hours prior to cisplatin was associated with an increase in 24-hour retention of platinum-DNA adducts [14]. Cisplatin 24 hours prior to gemcitabine was associated with significantly more leucopenia than the reverse sequence. Nonhematological toxicity consisted of grade 1-2 nausea, vomiting, and fatigue and was schedule independent. The maximal tolerated dose (MTD) when gemcitabine was followed by irinotecan was 1,000 and 60 mg/m² respectively. Synergistic activity was maximal when the interval between 5-FU and cisplatin administration was at least 24 hours. A significant reduction in DNA interstrand cross-link removal occurred in cells exposed to cisplatin alone or immediately preceded by 5-FU. This finding suggests that 5-FU modulates the repair of platinum-DNA adducts thereby potentiating antitumor activity. The response and survival outcomes associated with G-FLIP in this analysis of patients with treated adenocarcinoma of the exocrine pancreas exceed outcomes that would be expected with irinotecan alone. The reinduced efficacy of gemcitabine, 5-FU, and cisplatin as second-line therapy in this series challenges the traditional practice of switching to different drug classes upon disease progression.

By comparison, second-line G-FLIP utilized a sequence and schedule of gemcitabine, 5-FU, leucovorin, and cisplatin identical to first-line combination GFP. The only modification was the addition of irinotecan, inserted after gemcitabine on day 1. Irinotecan may overcome pancreatic cancer drug-specific resistance mechanism to either 5-FU, gemcitabine, or cisplatin.

6. Conclusion

Three and four drug regimens have recently reported good patient tolerability. A 26% response rate, 39% CBR, median disease-free survival of 5.4 months, and median overall survival of 6.9 months has been attained with 5-FU bolus and infusion, leucovorin, gemcitabine, and oxaliplatin []. Further prospective trials will explore the use of the G-FLIP regimen as initial therapy for patients with metastatic pancreatic cancer. In addition, the feasibility and efficacy of G-FLIP in gastric cancer, cholangiocarcinomas, and other bile duct tumors will be explored. Finally, Irinotecan combined with Gemcitabine, 5-Fluorouracil, Leucovorin and Cisplatin (G-FLIP) is an heavily pretreated in patients with disease likely to be responsive to the drugs contained in this combination. Our mathematical results shows G-FLIP drug

combinations are well tolerated option. We conclude that our mathematical result that the figure 2.1 is well fitted in the Skew logistic distribution.

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