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A Mathematical Model for Role of Gemcitabine and Carboplatin in Intensively Pretreated Patients with Metastatic Breast Cancer Using Bivariate Sinh-Normal Distribution Model

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Abstract: **In this paper we introduce bivariate sinh-normal distribution, which has seven parameters. Due to presence of seven parameters it is a very flexible distribution .Different properties of this new distribution has been established. We consider a bivariate model which can be obtained by transforming the sinh-normal distribution and it is a generalization of the bivariate Birnbaum-Saunders distribution. Several properties of the bivariate Birnbaum-Saunders distribution can be obtained as special cases of the proposed generalized bivariate Birnbaum-Saunders distribution. Patients with metastatic breast cancer (MBC) are increasingly exposed to anthracyclines and taxanes either during treatment of primary breast cancer or during initial therapy of metastatic disease. The combination of gemcitabine plus carboplatin is a generally well-tolerated and effective regimen that provided sustained disease control in intensively pretreated breast cancer patients. Specifically after previous exposure to anthracyclines and/or the taxanes, this regimen can be considered as an active treatment option which offers a favorable balance between efficacy and tolerability. Combination of chemotherapy with gemcitabine and carboplatin is an effective and generally well tolerated treatment option for intensively pretreated patients with MBC. Due to a considerable incidence of severe thrombocytopenia it would be reasonable to consider starting gemcitabine at the lower dose level of 800 mg/m^2. Our Mathematical result shows gemcitabine and carboplatin drug combinations are well tolerated treatment option. The medical curve and Mathematical curve for disease control is higher than the probability density functions which are monotonic functions.**

Keywords: **Gemcitabine, Carboplatin, Metastatic Breast Cancer, Sinh-Normal Distribution, Bivariate Birnbaum-Saunders Distribution.**

I. INTRODUCTION

As anthracyclines and also taxane-based regimens have become a standard of care for patients with primary breast cancer in the neo-adjuvant and adjuvant setting, the number of patients who have already been exposed to these drugs in the metastatic stage is increasing.Hence,the evaluation of alternative treatment strategies not cross-resistant to anthracyclines or taxanes is mandatory. At the same time, it is important to ensure that efficacy is improved at the lowest cost to quality of life. Gemcitabine as a single agent has induced overall response rates of 0-37% in first-line treatment, whereas the response rates in the second-or third-line therapy were 26 and 13% [2,3,5,917].In studies limited to second-or third-line therapy after anthracycline and/or taxane exposure, response rates of 0-29% and median time to progression of 2-6 months were reached[3,9,17]. Gemcitabine is an excellent choice for combination therapy because of its unique mechanism of action and its favorable profile of side effects. The Combination of gemcitabine and cisplatin was shown to be effective in several trials, inducing response rates between 30 and 52% in patients pretreated with taxanes and/or anthracyclines[4,6,10,15].To improve on tolerability and feasibility of the regimen, carboplatin may be the more appropriate choice for treatment of metastatic disease. In four phases II trials of previously untreated patients with metastatic breast cancer (MBC), single agent carboplatin induced objective response rates between 8 and 35% .Studies performed in various solid tumor types indicate comparable activity of cisplatin and Carboplatin.

It appears that resistance to platinum salts is induced by pretreatment, possibly by an up regulation of DNA repair, Gemcitabine, a known inhibitor of DNA repair, may overcome this form of resistance and thus provides an excellent rationale for the combination of both agents. Exposure to platinum salts causes an activation of DNA repair Polymerases and therapy enhances the incorporation of gemcitabine triphosphates into DNA repair patches. Once integrated into DNA, gemcitabine is not readily recognized and excised by proofreading exonucleases and may trigger signaling pathways leading to apoptosis. Several Considerations support the use of gemcitabine and a platinum salt in the salvage treatment of MBC. First, in vitro studies indicate additive or synergistic activity which was most pronounced in platinum-resistant cell lines and was found to be due to an increased formation and an impaired repair of platinum–DNA adducts [13,18].Second, gemcitabine and carboplatin are usually not included into adjuvant or neo-adjuvant chemotherapy. Therefore, resistance to either drug is unlikely to occur. Third, studies investigating the combination have shown minimal overlapping toxicity suggesting an acceptable toxicity profile even in intensively pretreated patients [9,11,12].Finally, the addition of trastuzumab to gemcitabine/carboplatin might form an effective triplet combination.

The present multicenter phase II study was aimed to evaluate the efficacy and tolerability of gemcitabine applied on days 1 and 8 plus carboplatin applied on day 1

every 3 weeks in previously treated patients with MBC. Thirty-nine patients with histologically confirmed MBC were recruited to participate in a study with a treatment protocol approved by the local ethics committee. All patients were required to give written informed consent prior to study entry. Prior treatment with chemotherapy, hormonal therapy, immunotherapy or local radiotherapy was allowed. Patients were not eligible for study enrolment if they were pregnant, lactating or refused effective contraception, and if they had bone metastasis only, known brain metastases or a secondary malignancy. Administration of other cytotoxic, immune or hormonal agents or radiation therapy was not permitted during the study, with the exception of contraceptives, corticosteroids given as antiemetic treatment, or local palliative radiation.

Patients were evaluated on a regular basis during treatment. The following assessments were performed before each 3-week cycle: physical examination, complete blood count, serum chemistry and assessment of toxicities. During the initial phase of treatment, complete blood counts were performed twice weekly to determine the nadir values. If the hematological values had not recovered by the time of schedule treatment, the complete blood count was repeated every week until recovery of leukocyte count to $3.0x10^9$/I and platelets to greater than or equal to 100 x 10^9/I. Treatment consisted of gemcitabine 1,000 mg/m^2 given as a 30-min infusion on days 1 and 8 and carboplatin AUC 4 given as a 1-hour infusion on day 1 of a 3-week treatment cycle. Treatment was continued until disease progression or the occurrences of unacceptable toxicity. The primary objective of the study was to determine the objective response rate to the study treatment. Secondary end points included time to progression, survival and toxicity. The study was planned to distinguish between a uninteresting response rate of 10% (null hypothesis) and a interesting response rate of 30%(alternative hypothesis).With the type I error being 5% and the type II error 10%,18 patients were to be enrolled during the first step and an additional 17 patients during the second step. If 2 or less responses occurred among the first 18 patients or 6 or less responses in the total population of 35 patients, the treatment had to be judged ineffective and enrolment stopped. If 7 or more responses were observed in the total patient population, the study treatment was judged effective. Assuming a dropout rate of 10% enrollment of a total of 39 patients was planned. The 95% confidence interval (CI) for the overall response rate was determined on the basis of the two-stage design. Time-to-event end points were calculated according to the method of Kaplan and Meier using STATISTICA software. Patients who received at least one treatment cycle were evaluable for toxicity, and those who had received at least two treatment cycles or those who progressed after the first cycle were evaluable for response.

II. APPLICATION

Thirty-nine eligible patients were recruited from 12 German centers. All patients were evaluable for response, toxicity and survival. Median age was 60 years. All patients had previously received chemotherapy and 33 of them had received up to 5 prior chemotherapy regimens for metastatic disease. Twenty-six patients (67%) had received anthracyclines and 25 patients(64%) both, an anthracycline and a taxane-based regimen. Prior endocrine therapy in hormone receptor-positive patients had been applied to 31 patients (80%).26 patients (67%) had received tamoxifen, and 20 patients had received an aromatase inhibitor (51%).35 patients presented with visceral metastases (90%) and 31 patients (79.5%) had more than one metastases site. A total of 207 cycles of gemcitabine and carboplatin were delivered. Patients received a median number of 5 cycles (range: 1-12 cycles).Median duration of treatment was 3.8 months (range: 0.5-9.3 months).Dose reductions, delays and omissions occurred in 131 (63%), 65 (31%) and 36 (17%) cycles, respectively. All patients were evaluable for efficacy. One patient achieved a complete response and 11 patients (28.2%) a partial response, for an objective response rate of 30.8% (95% CI: 17.0-47.6%).Overall, disease control rate (objective response plus stable disease) was 61.5% (95% CI:44.6-76.6%).Disease stabiliz-ation was achieved in 12 patients (30.8%).Overall, disease control rate was 61.5%.Disease stabilization was achieved in 12 patients, lasting for more than 3 months in 11 (28.2%) and for more than 6 months in 7 patients(17.9%).

The median time to first observation of an objective response was 2.6 months (95% CI: 1.3-5.1 months). Median duration of response was 3.3 months (95% CI: 3.0-5.8 months), and median time to progression was 5.3 months (95% CI: 2.6-6.7 months).The median overall survival was 13.2 months (95% CI: 8.7-16.7 months).Time to progression and overall survival are shown in the Figure (2.1).

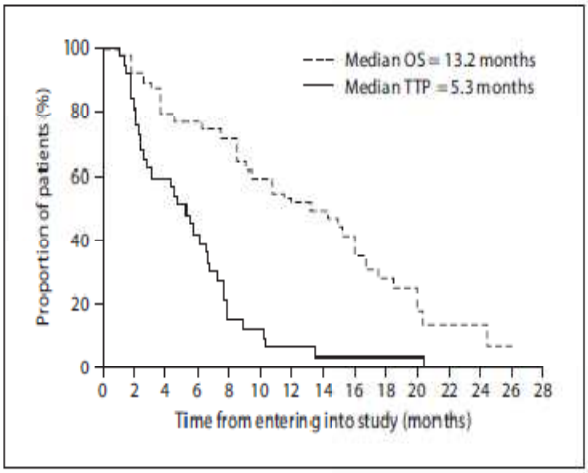


Fig.2.1.Time to progression (TTP,–-)and overall survival (OS,---)

III. Mathematical Model

The main aim of this paper is to introduce bivariate sinh-normal (BSHN) distribution, which is a natural extension of SHN distribution of one dimension to two dimensions. Recently, Kundu et al. [7] introduced a bivariate Birnbaum-Saunders distribution. It is observed that the bivariate log- Birnbaum-Saunders distribution can be obtained as a special case of the BSHN distribution. The proposed BSHN distribution has seven parameters, and doe to presence of two location, two shapes, two scales and one correlation parameters, it is a very flexible model. After proper normalization, as the shape parameters converge to zero, it approaches to a standard bivariate normal distribution. The probability density function (PDF) of BSHN,can be both unimodal or bimodal depending on the shape parameters. Due to presence of the two shape parameters, it is more flexible than the bivariate normal distribution. The marginals of BSHN are SHN distributions and the conditional distribution also can be obtained in closed form. We introduce a new bivariate distribution, which can be obtained by transforming the BSHN random variable. The new distribution is a generalization of the bivariate Birnbaum-Saunders distribution introduced by Kundu et al. [7] and we call it as the bivariate generalized Birnbaum-Saunders distribution. We establish different properties of the generalized Birnbaum-Saunders distribution and it is observed that several properties of the bivariate Birnbaum-Saunders distribution can be obtained as special cases of the proposed distribution.

Suppose Y ~ SHN (α,σ,μ) then the probability density function (PDF) becomes

$$f_Y(y;\alpha,\sigma,\mu)=\Phi(a(y;\alpha,\sigma,\mu))A(y;\alpha,\sigma,\mu);\quad y\in R$$

Here Φ (.) is the PDF of a standard normal random variable .

By simple transformation, it follows that if Y ~ SHN (α,σ,μ), then

$$Z=\frac{2}{\alpha}\sinh\left(\frac{y-\mu}{\sigma}\right)-N(0,1)$$

Here N (0,1) denotes a standard normal random variable.

Rieck [14] has established the following properties of a SHN distribution. The PDF of SHN is symmetric about the location parameter μ.The distribution is strongly unimodal for $\alpha\le 2$ and it is bimodal if $\alpha>2$ .It can be easily seen using L'Hospital's rule, that if

Y~ SHN(α,σ,μ) then

$$\frac{2(Y-\mu)}{\alpha\sigma}\rightarrow N(0,1)\ as\ \ \alpha\rightarrow 0$$

It is an absolute continuous distribution with the PDF

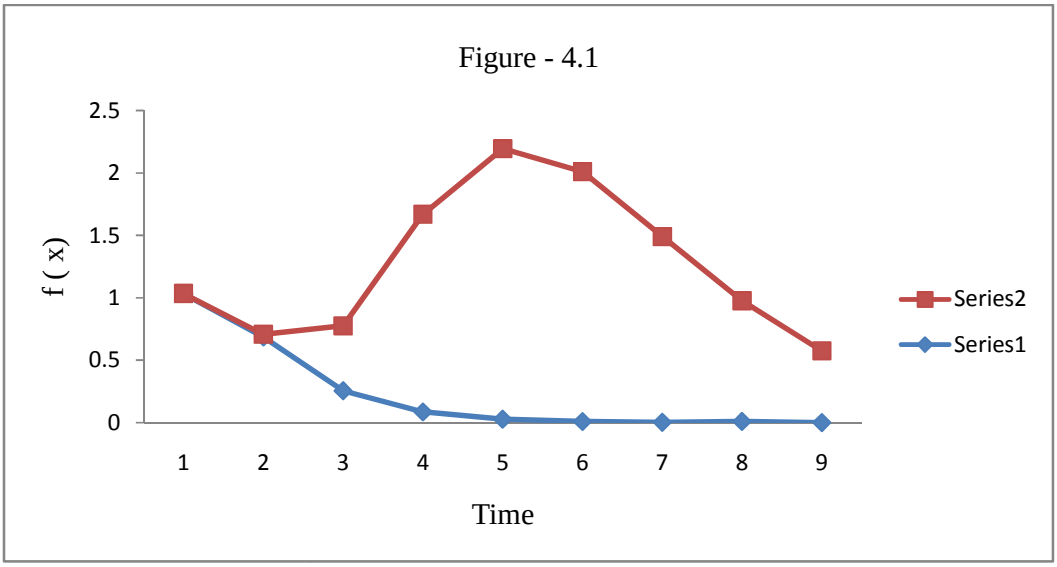
$$f_T(t;\alpha,\beta)=\frac{1}{2\sqrt{2\Pi}\alpha\beta}\left[\left(\frac{\beta}{t}\right)^{\frac{1}{2}}+\left(\frac{\beta}{t}\right)^{\frac{3}{2}}\right]\exp\left[-\frac{1}{2\alpha^2}\left(\frac{t}{\beta}+\frac{\beta}{t}-2\right)\right],\ \ t>0$$

Here α is the shape parameter and β is the scale parameter.

A standard BSHN random variable has the PDF which is centred at (0,0) and it is symmetric around (0,0).It is observed that the surface of the PDF can be unimodal,bimodal or multimodal depending on the parameter values.

IV. Mathematical Results

Figure - 4.1



V. Discussion

With the increasing use of anthracycline and taxane - based regimens in the adjuvant and neoa-djuvant setting and their established application in the treatment of the advanced and metastatic stages of breast cancer, there is a clear need for non- cross-resistant further-line regimens. While there is no established standard of chemotherapy for anthracycline and taxane-Pretreated patients, capecitabine has become a widely accepted agent in this treatment setting. In phase II and III trials response rates in the range of 26-52% and time to progression of 3.6-8.9 months were reported. The premedical rationale for a combination of gencitabine with a platinum analog is supported by the synergistic interaction of both agents [1]. Several medical studies performed with various schedules have demonstrated that the combination of gemcitabine and cisplatin is highly active not only the first –line treatment, but also in patients previously exposed to anthracycline and/or taxanes. While a formal comparison of carboplatin and cisplatin has never been performed in MBC, the available evidence suggests a better tolerability of carboplatin. Due to its lower emetogenic and nephrotoxic potential carboplatin may be specifically preferred in intensively pretreated patients. Moreover, time-consuming hydration regimens can be avoided with carboplatin. The present study evaluated a 3-week regimen, where gemcitabine was applied on days 1 and 8, while carboplatin was given on day 1.Most patients had undergone previous treatment with anthracyclines (67%) and/or taxanes (64%).The efficacy of gemcitabine plus carboplatin reached the predefined endpoint of a clinically relevant activity. The median duration of most responses and disease stabilizations was 3.3 and 6.8 months, respectively. The median time to progression was 5.3 months resulting in a median overall survival of 13.2 months. Comparable results have also been reported by Nasr et al.[12] who investigated a schedule where gemcitabine and a great dose of carboplatin were applied in a 3-week regimen. The combination was given to 30 MBC patients as a second-line treatment. The overall response rate was 30% and median time to progression was 4.8 months. Main grade 3/4 hematological toxicities were neutropenia in 50% of patients, anemia in 26.6% and thrombocytopenia in 30% of patients. The same schedule was evaluated by Silva et al.[16] in 19 comparably pretreated MBC patients yielding an overall response rate of 21.5% and a median overall survival of 7.5 months. Main hematological toxicities included anemia, neutropenia and thrombocytopenia in 5% of patients. Nagourneyetal.[11] reported a‘repeating doublet’regimen, where gemcitabine and carboplatin were both applied on days 1 and 8 of a 3-week regimen. Ten evaluable patients with first or second recurrence of MBC had received the schedule with an overall response rate of 50% and a median time to progression of 5 months. Most commonly reported grade 3 and 4 side effects were neutropenia and thrombocytopenia. The treatment associated toxicity profile in our study was generally acceptable. Hematological toxicity, mainly leukopenia and thrombocytopenia, occurred in 26 and 23% of the applied cycle respectively. The rate of febrile neutropenia was low as compared to an incidence of 20% in the study by Nasr et al[12].As a consequence, a median of 5 cycles could be administered without significant delays or dose reductions. Nevertheless, 38% of the patients required hematopoietic growth factor support. This is a part explained by the intensive pretreatment observed in most of the patients. Thus, for the considerable incidence of severe thrombocyt-openia it would be reasonable to consider starting gemcitabine at the lower dose level of 800 mg/m^2. Symptomatic adverse events such as nausea/vomiting or asthenia were generally mild to moderate. There was no patient who developed renal dysfunction .Certainly, an optimal regimen of gemcitabine/carboplatin for intensively pretreated MBC patients has not been determined in a comparative fashion.It appears, however, that the application of carboplatin on day 1 may be preferred to the repeating doublet regimen since the latter was associated with a higher incidence of hematological toxicity.

VI. Conclusion

Finally, the combination of gemcitabine plus carboplatin is a generally well-tolerated and effective regimen that provided sustained disease control in intensively pretreated breast cancer patients. Specifically after previous exposure to anthracyclines and/or the taxanes, this regimen can be considered as an active treatment option which offers a favorable balance between efficacy and tolerability. Combination of chemotherapy with gemcitabine and carboplatin is an effective and generally well tolerated treatment option for intensively pretreated patients with MBC. Due to a considerable incidence of severe thrombocytopenia it would be reasonable to consider starting gemcitabine at the lower dose level of 800 mg/m^2.Our Mathematical results shows gemcitabine and carboplatin drug combinations are well tolerated treatment option. The medical curve and Mathematical curve for disease control is higher than the probability density functions which are monotonic functions.

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