CHAPTER 7

MATHEMATICAL MODEL ON GnRH ANTAGONISTS TO ENHANCE THE PROSTATE CANCER BEHAVIOR

7.1 Introduction

Consider a mathematical model on GnRH antagonists, which is suitably simple to be of practical use in the clinical trials will ultimately establish their efficacy in comparison to other pharmacotherapies. Therefore, continuing development and renement is needed to improve prostate cancer treatment. GnRH antagonists offer a new means of treatment by directly blocking GnRH receptors. Advantages of GnRH antagonists include lack of the initial stimulation of gonadotropin and testosterone production, lack of gonadotropin micro surges and sustained follicle-stimulating hormone suppression; is advantages include increased histamine release.

This review discusses advantages and disadvantages of the GnRH antagonists currently in development. A mathematical model based on a statistical system approach, has been implemented and tested on the basis of a long-term experimental data set, with the aim of analyzing the performance and clinical outcome of an existing medical ward, and predicting the effects that

possible readjustments and/or interventions on the structure may produce on it **[22].**

Although it has been proven that in treating prostate cancer, the effectiveness of GnRH-agonist treatment is similar to that of surgical castration, reports in the literature indicate a lack of steroidogenic suppression under agonist therapy. One study reported that of 40 men treated with depot injections of the agonist leuprolide, two (5%) did not reach a testosterone level of 1.9 nmol/l (0.5 ng/ml) and five (13%) did not reach levels of 0.7 nmol/l (0.2 ng/ml).

In another study, 9% of patients undergoing agonist treatment did not achieve testosterone levels in the castrate range **[68].** A reasonable assumption is that failure to suppress to castrate levels might be 5–10%, whereas converting microsurges to non-castrate values might occur in >20%. The reasons for agonist treatment failure have been suggested as sterile abscess at the site of agonist implant **[56,132],** pituitary gonadotroph adenoma or obesity.

In some cases, the failure of agonists to achieve castrate levels has been specific to the agonist used, and the formation of antibodies against agonists or involvement of GnRH -R mutations have also been discussed as potential reasons for failure. Monitoring testosterone levels in non-responsive patients is important because incomplete or failed suppression during agonist therapy

might explain the marginally better survival rates of patients on complete androgen blockade compared with those on agonist monotherapy **[147].**

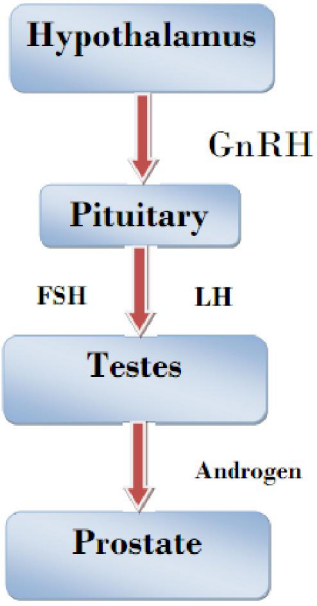

Figure 7.1.1 Mechanism of GnRH antagonist action

The GnRH antagonist degarelix has been administered to over 1500 patients with no reported cases of immediate-on set systemic allergic reactions to date. The most frequently reported adverse effect was hot flashes in 32% of patients, which is an expected androgen withdrawal symptom.

In two one-year, phase II degarelix dose-finding studies **[12,147],** a rapid reduction in testosterone to <1.7 nmol was seen after three days in 91% of patients receiving 230 mg and after one month in 88% of patients receiving 200 mg in both studies, low testosterone levels were maintained through-out, and there was no evidence of testosterone surge Preliminary results are also now

available from a phase III comparative trial of degarelix (two dosing regimens: 240/160 mg and 240/80 mg) versus leuprolide 7.5 mg (withor without bicalutamide anti-androgen flare protection) in610 patients with prostate cancer. Both doses of degarelixwere shown to be non-inferior to leuprolide with respect tomaintaining testosterone at castrate levels (1.76nmol/l0.5 ng/ml]) for up to one year. At day 3, castrate levels were achieved in 95% of degarelix-treated patients compared with 0% of the leuprolide patients **[137].**

A total of 80% of patients treated with leuprolide experienced a testosterone surge, and no patients in either degarelix group experienced such a surge. After 14 days of treatment, reductions in median PSA levels were 3.5times greater in the degarelix groups than in the leuprolide group. The safety profiles of the treatments for both thera-pies were in accordance with androgen-deprivation therapy, although the subcutaneous degarelix injection was associated with more injection-site reactions than the intramuscular leuprolide. However, the majority occurred at first injection and were mostly of mild-to-moderate intensity.

7.2 Mathematical model and Assumptions

The endocrine system is very difficult, and the secretion of hormones relating to reproduction is strongly regulated by several factors. This approach is to use a simple representation of the system that focuses on the interactions of

GnRH. For simplicity, a mathematical model is developed in which each variable represents the GnRH antagonist action.

Let the efficacy of GnRH analogue therapy for prostate cancer be V and let the intial stimulation of gonatropin and testosterone production LH be c(0). Let suppression of LH secretion be introduced to prostate cancer treatment at a constant rate I. LH secretion is also removed from due to the physiological needs of the treatment at a rate proportional to c(t), so it gives

$$G\frac{dc}{dt} = I - kc \tag{7.1}$$

Now let a dose GnRH D of a medicine be given to a patient at regular intervals of duration T each. The medicine also disappears from the system at a rate proportional to c (t), the concentration of the medicine in the treatment, then

$$G\frac{dc}{dt} = -kc \tag{7.2}$$

Integrating

$$c(t) = D\exp\left(-\frac{k}{G}t\right),\ 0 \le \mathrm{t} < \mathrm{T} \tag{7.3}$$

At time T, the residue of the first dose is D $\exp\left(-\frac{k}{G}t\right)$ and now another dose D is given so that,

$$c(t)=\left(D\ \exp\left(-\frac{k}{G}t \right)+D \right)\ \exp\left(-\frac{k}{G}\ (t-T) \right) \tag{7.4}$$

$$=D\exp\left(-\frac{k}{G}t \right)+D\ \exp\left(-\frac{k}{G}\ (t-T) \right) \tag{7.5}$$

$T \le t \le 2T$

The first term gives the residual of the first dose and the second term gives the residual of the second dose. Proceeding in the same way, after *n* doses

$$c(t)=D\ \exp\left(-\frac{k}{G}t \right)+D\ \exp\left(-\frac{k}{G}\ (t-T) \right)+D\ \exp\left(-\frac{k}{G}\ (t-2T) \right)+\cdots + D\ \exp\left(-\frac{k}{G}\ \left(t-\overline{n-1}T \right) \right) \tag{7.6}$$

$$=D\ \exp\left(-\frac{k}{G}t \right)\left(1+\exp\left(\frac{k}{G}T \right)+\exp\left(\frac{2k}{G}T \right)+\cdots+\exp\left((n-1)\frac{k}{G}T \right) \right) \tag{7.7}$$

$$=D\exp\left(-\frac{k}{G}t \right)\frac{\exp\left(n\frac{k}{G}\mathrm{T} \right)-1}{\exp\left(\frac{k}{G}\mathrm{T} \right)-1},(n-1)T \le t < nT \tag{7.8}$$

$$c(nT-0)=D\frac{1-\exp\left(-\frac{k}{G}nT \right)}{\exp\left(\frac{k\mathrm{T}}{G} \right)-1} \tag{7.9}$$

$$c(nT+0) = D\frac{\exp\left(\frac{k\mathrm{T}}{\nu}\right) - \exp\left(-\frac{k}{\nu}nT\right)}{\exp\left(\frac{k\mathrm{T}}{\nu}\right) - 1} \qquad 7.10$$

Thus the concentration never exceeds $D \Big/ \left(1 - \exp\left(-\frac{kT}{G}\right)\right)$. The graph of c (t) is shown in section. Thus in each interval, concentration decreases. In any interval, the concentration is maximum at the beginning of this interval and thus maximum concentration at the beginning of this interval goes on increasing as the number of interval increases, but the maximum value is always below $D/\left(1-e^{-\mathrm{kT}/G}\right)$. The minimum value in an interval occurs at the end of each interval. This is also increases, but it lies below $\mathrm{D}/(\exp\ (\mathrm{kT}/G)-1)$.

The concentration curve is continuous and has points of discontinuity at T, 2T, 3T…

By injecting Leuprolide or related testosterone outflows in blood and fitting curve to the data, the proposed model would estimate the parameter based on pre-processed data **[22].**

7.3 Application

Several GnRH antagonists currently in development for prostate cancer include teverelix and ozarelix, which are in phase II development, and acyline and cetrorelix, which have completed phase I studies. A single dose of teverelix

(90 mg) on three consecutive days in 14 patients with prostate cancer caused rapid decreases in testosterone, LH and PSA, with castrate levels of testosterone achieved and maintained in all patients for at least four weeks.

Preliminary data show that the mean onset of castration levels was apparent at 1.77 days after the first teverelix dose and sustained for a mean of 55.32 days .Cetrorelix has been shown to improve symptoms in two phase I studies in patients with advanced prostate cancer**[68,77 ,132].**

Cetrorelix (500 mg twice daily) produced a major fall in free testosterone levels after the first dose, with maximum suppression after 6–12 h. PSA levels also gradually fell, achieving near-normal levels by week 6; patients experienced a decrease in bone pain and relief of urinary out flow obstruction . In the second study, in five patients with advanced prostate cancer and metastatic spinal cord invasion-induced paraplegia, all patients experienced marked reductions in prostate volume and improvements in bladder function and neurological symptoms, and were able to walk with the aid of a cane after three months of treatment. Mean testosterone levels were significantly reduced at 12 h ($p<0.005$) and maintained throughout therapy **[58].**

Various orally active GnRH antagonists are undergoing early clinical evaluation for their potential use in treating hormonal disorders, including prostate cancer. The non-peptide antagonist NBI-42902 is in phase I

development for prostate cancer **[148].** Results from a dose-ranging study for MER-104, an oral formulation of the injectable GnRH antagonist acyline using gastrointestinal permeation enhancement technology (GIPETTM), indicate that this formulation has potential in hormone-sensitive prostate cancer **[132].**Although GnRH antagonists do not produce flare, they do have to be given at higher doses than GnRH agonists and, so, there is a potential for greater pain at injection sites and a theoretically greater risk of side-effects.

How-ever, clinical trials to date have demonstrated that GnRH agonists and antagonists have broadly similar tolerability profiles, consistent with androgen deprivation. Histamine-associated allergic reactions are known side-effects of peptide GnRH antagonists (transient oedema andsystemic or local anaphylactoid reactions were note during early development **[56];** however, newer GnRH antagonists, including degarelix, have a lower potential for histamine release than other GnRH antagonists **[22].**Increased cost could also be an issue with GnRH antagonists, but this needs to be weighed against the benefits of a single agent compared with combination therapy (agonist plus anti-androgen)

7.4 Results

Figures shows the Efficacy of GnRH antagonists deregarelix or vehicle on LH and Testosterone.

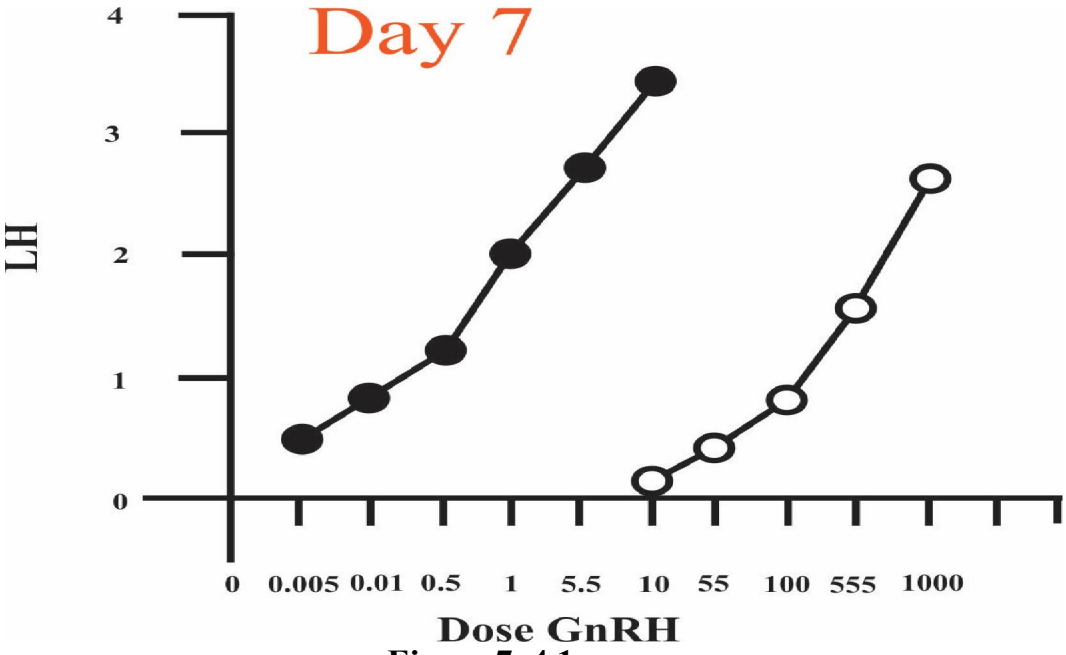

Figure 7 .4.1

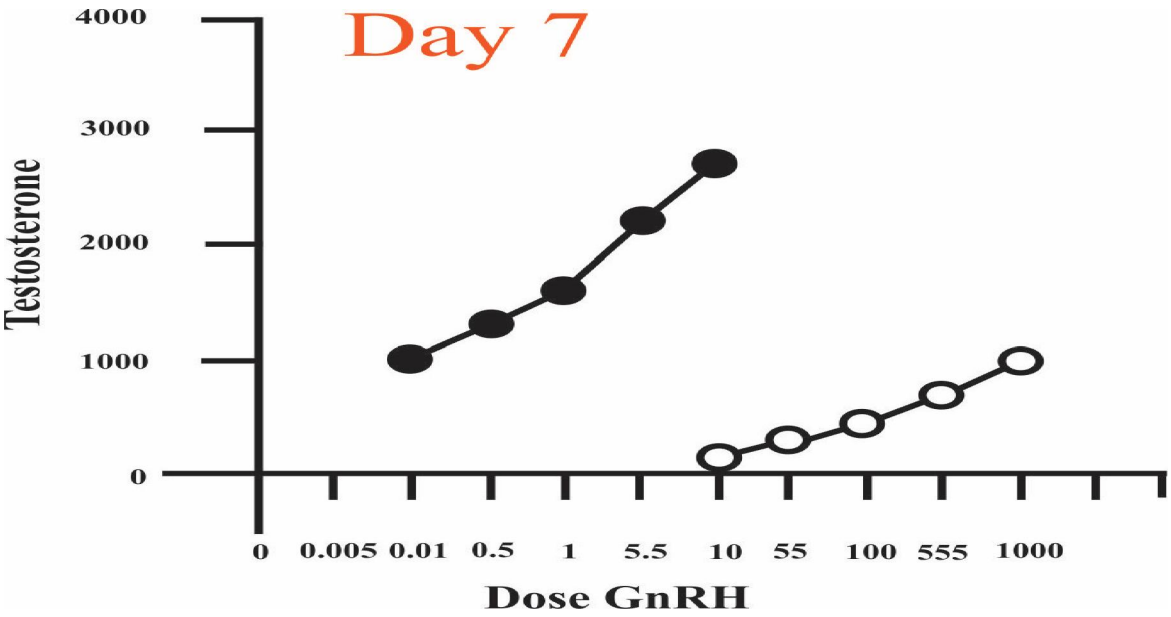

Figure 7.4.2

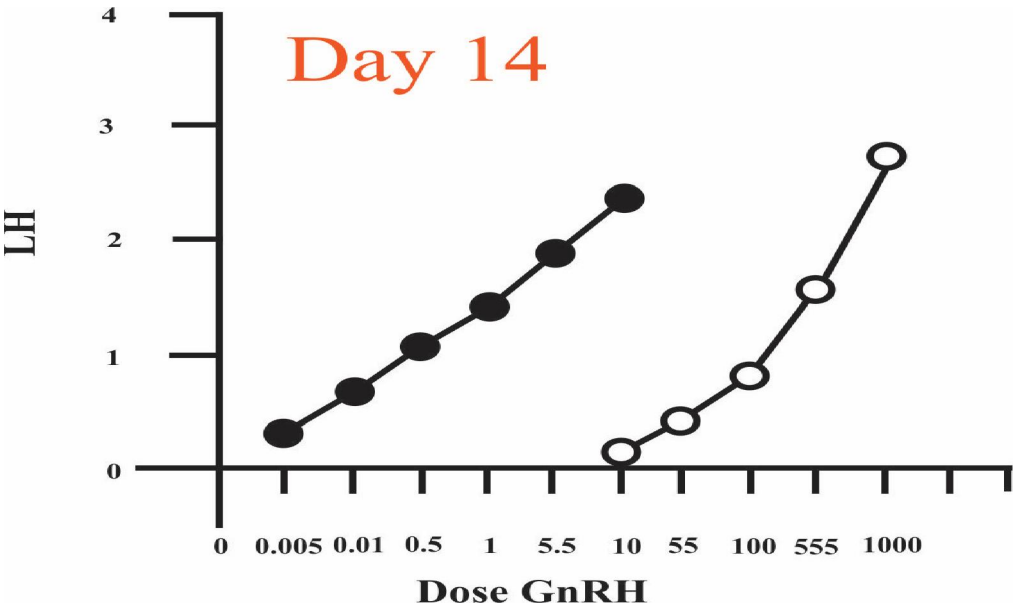

Figure 7.4.3

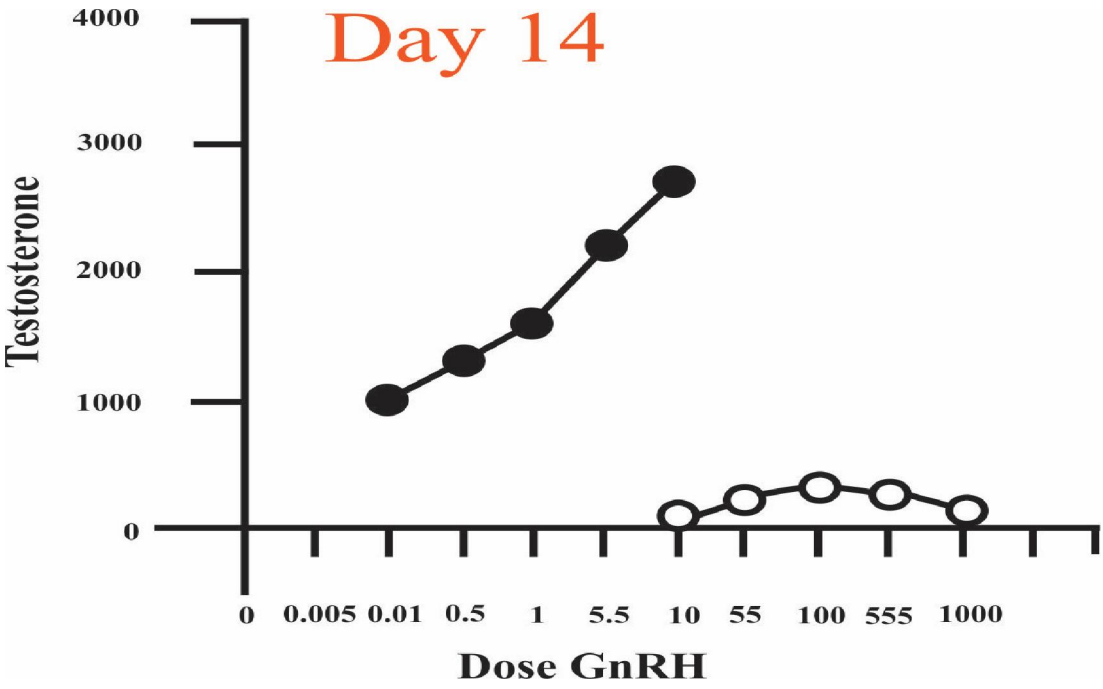

Figure 7.4.4

Fig 7.4.1-7.4.4 Efficacy of GnRH antagonists (7-Days and 14-Days) deregarelix or vehicle on LH and testosterone

7.5 Conclusion

The raw data and mathematical models provided more rapid and sustained suppression of serum LH and testosterone with antagonist treatment. A recent phase III trial comparing degarelix with leuprolide has demonstrated non-inferiority of the GnRH antagonist to leuprolide with respect to maintaining suppression of testosterone for a year study duration. Further mathematical models controlled trials directly comparing these two methods of gonadotropin suppression will help to establish the optimal approach to the long-term management of prostate cancer.