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COMPARATIVE HAEMATOLOGY AND RENAL TOXICITY OF ALECTINIB AND DAUNORUBICIN IN RABBIT

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Abstract:-

Alectinib is an anthracycline antibiotic anticancer medication that is commonly used to treat a variety of haematological and solid tumour malignancies, such as breast cancer, leukaemia, and sarcomas. Daunorubicin and doxorubicin, two anthracycline antibiotics, are among the most effective cytotoxic anticancer medications. Both experimental groups displayed haematotoxicity, which was mainly exhibited by aplastic anaemia. A significant reduction in body weight (by 45.2%) and a high rate of early death (100% versus 36.4%) were indicators of alectinib's higher overall toxicity, particularly nephrotoxicity when compared to daunorubicin. The administration of daunorubicin (DAU) to rabbits was tested. There were three kinds of animals used: Alectinib (1.25 mg/kg, ear vein) was given to 3 mice in the control group; Daunorubicin (DAU, 1.6 mg/kg ear vein) was given to 3 animals in the model.

Keyword :- Alectinib, Daunorbicin, Renal Toxicity, Hematology

Introduction:-

The cytotoxic anticancer medications of the second generation include the anthracycline antibiotics daunorubicin and alectinib. Acute lymphocytic and acute myeloid leukaemia are treated with the chemotherapy drug dunorubicin [1]. The body's ability to proliferate and spread cancer cells is slowed by dunorubicin [2]. Their chemical compositions barely differ by one hydroxyl group on carbon-14. Despite this, there are significant variances in how they are used in clinical settings. Doxorubicin has a broad spectrum of powerful activity against many different malignancies, including a variety of solid tumours, whereas daunorubicin has been employed exclusively in the treatment of acute leukaemia [3].1 Another significant limiting issue for the use of anthracyclines is bone marrow depression. The most frequent and the most serious type of chronic dilated. Despite the fact that anthracycline-treated individuals had varying degrees of renal lesion, renal toxicity was discovered at cumulative alectinib doses of more than Rats and mice with anthracycline-induced nephropathy have been employed as models for the investigation of the pathophysiological mechanisms underlying nephropathy[7]. Numerous studies have described the long-term harmful consequences of both the main anthracyclines and those that are structurally close to them, namely daunorubicin and alectinib. because the studies' experimental designs varied [8].It is challenging to compare the chronic toxicity of the aforementioned anthracyclines [9].

This experimental investigation used a similar study design on rabbits to compare the long-term harmful effects of daunorubicin and doxorubicin. For ten weeks, both medications were given intravenously once a week at a dose of 3 mg/kg [10]. In our investigation, we monitored body weight, fundamental hemodynamic parameters,

common biochemical parameters, and haematological parameters. At the conclusion of the trial, a kidney and liver histology investigation was also carried out. DAU was hence selected for this research [11]. The purpose of this study is to evaluate a rabbit model of DAU-induced kidney toxicity and to describe various techniques for assessing and quantifying experimentally caused cardiac damage. Additionally, DEX is assessed as a [12]. This experimental study compared the long-term detrimental effects of daunorubicin and doxorubicin in rabbits using a similar study design. Both drugs were administered intravenously once a week for ten weeks at a dose of 3 mg/kg [10]. We tracked body weight, basic hemodynamic parameters, widespread biochemical parameters, and haematological parameters during our experiment. A liver and renal histology investigation was also completed after the trial. DAU was hence chosen for this study [11]. This work aims to investigate a rabbit kidney toxicity model created by DAU and to present alternative methods for evaluating and measuring experimentally induced cardiac damage. DEX is additionally rated as a [16]. Multidrug-resistant (MDR) cancer cells develop concurrent resistance to a number of structurally and functionally unrelated anticancer medicines. The FDA has approved the use of alectinib, an orally active ATP-competitive anaplastic lymphoma kinase (ALK) inhibitor, for the treatment of individuals with NSCLC that has tested positive for ALK [17]. The mainstay of treatment for many types of human cancer is chemotherapy. Sadly, MDR frequently poses a barrier to effective chemotherapeutic cancer treatment [18]. Multidrug-resistant (MDR) cancer cells develop simultaneous resistance to a number of structurally and functionally unrelated anticancer medications [19]. A cancer drug called dunorubicin prevents the growth and metastasis of cancer cells in the body. The drug daunorubicin is used to treat leukaemia, a kind of blood cancer. There are further uses for dunorubicin besides.
heart disease
kidney disease
liver disease
a weak immune system (caused by disease or by using certain medicines) or
if you have ever been treated with doxorubicin, epirubicin, idarubicin, mitoxantrone, or liposomal daunorubicin
.
Using daunorubicin may increase your risk of developing other types of leukemia.

Used of drug

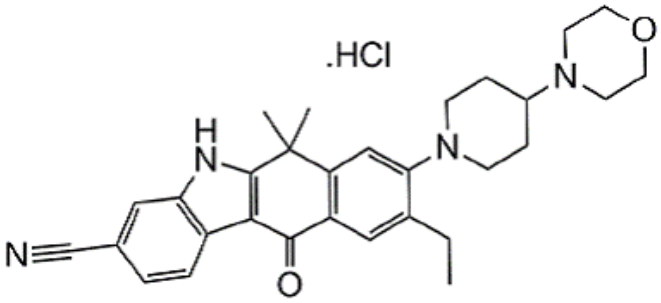
Acute myelogenous leukaemia (AML) treatment
Acute lymphoblastic leukaemia (ALL) treatment
Acute promyelocytic leukaemia (APL) treatment

Side effect of drug

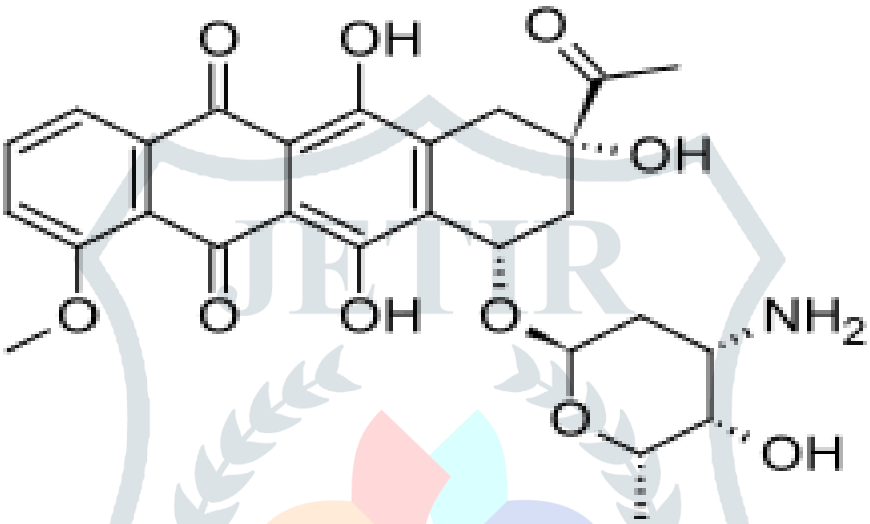
When it comes to the onset, duration, and severity of side effects, they are frequently predictable.

There are numerous ways to lessen or avoid negative effects.
The presence or intensity of a medication's adverse effects has no bearing on how well it works.

Low red blood cell count, or anaemia
fatigue and weakened state
increased SGPT, SGOT, and bilirubin levels in liver function tests
Hyperglycemia, or high blood sugar
Constipation
(hypocalcaemia) Low blood calcium levels
Edoema, or swelling
Reduced lymphocyte count (white blood cells that fight infection) and increased creatinine level
Nausea.
Red urine for one or two days after a dosage.



Alectinib



Daunorubicin

Alectinib:-
Formula for a chemical: C30H34N4O2
Weight: 482.6166

A class of substances is antineoplastic agents.

Daunorubicin:-
C27H29NO10 Chemical Formula
Weight 527.5199

A class of substances is antineoplastic agents.

Aim & Objective

Alectinib and Daunorobicin liver issues and haematological blood tests to assess rabbit liver function at least every two weeks for the first two months of treatment, as well as as needed during treatment, are the goal and objective of this study.

To analyzes the renal toxicity of Alectinib and Daunorobicin.

Creatinine
Blood Urea Nitrogen
White blood cell
Red blood cell
SGOT
SGPT

Material and methods:-

- We used medium-sized rabbits that typically weighed between 2-4 kg. All treatments were carried out under the direction of the Medical Faculty's Ethics Committee at Monad University in Hapur and in compliance with the "Guide for the care and use of laboratory animals" (1996). There were three groups of animals:
- Three groups of three rabbits each weighing between 2-4 kg were created. Rabbits received injections of
- Control group (n=3) - 0.9 % NaCI.
- Alectinib group (n=3) - a single dose of 1.6 mg/kg
- Daunorubicin group (n=3) - a dose of 1.25mg/kg for weekly/two time.

Rabbit of 2-4 kg were divided into three groups each group consisting of three animals. Rabbit is ear vein injected with drug and powder form drug are mixed in soluble liquid.

Animal Used

Group 1: - 0.9 % NaCI control (C)

9 G/L Sodium Chloride (sodium chloride injection) USP (NaCl) is present in 0.9% Sodium Chloride Injection, USP. It has 154 mEq/L of chloride and 154 mEq/L of sodium. There is a 1ml/kg body weight NaCl dosage. 9.0 g (154 m mol) of sodium chloride are dissolved in 1000 ml of water to create the solution.

Group 2:- weekly/two time dose of 1.6 mg/kg Alectinib

The fastest-proliferating cells, which are theoretically cancer cells, are killed when alexitinib interferes with DNA replication. After administration, a mechanism known as causes one chloride ion to be gradually displaced by water in order to give the alectinib. Because the internal chloride concentration is just 9–25% of the about 100 mm extracellular fluid chloride concentration, dissociation of the chloride is favourably favoured inside the cell.

Group 3:- Daunorubicin in a dose of 1.25 mg/kg for weekly/two time

Daunorubicin The pineal gland produces a hormone that controls the sleep cycle. Daunorubicin's impact in these tests has been contrasted with its kidney toxicity. Alectinib, DAU, or a vehicle (0.9% NaCl) will be administered chronically to three groups (N = 3/group) of 2-4 kilogramme rabbits. Alectinib 1.25 mg/kg and DAU 1.6 mg/kg medication doses or a vehicle will be infused into an ear vein twice per week.

Drug & Chemical

- Alectinib
- Daunorubicin
- Distilled water
- Normal saline
- Ethanol
- Propanol
- Methanol
- Sodium chloride
- Picric Acid
- Chloroform
- Centrifuge

Instrument & apparatus

- Needle
- Refrigerators
- Syringe and needle (1ml,2ml,5ml and 10 ml)
- Test tube Stand
- Ependrop
- WeightMachine
- Microscopy

- Haemocytometer slide
- Haemostosis analysis system
- Glebes
- Glass rod
- Beaker
- Creatinine test kit
- BUN test kit

Methodology

Study of place	:	Monad University, Hapur
Drug Name	:	Alectinib & Daunorubicin
Type of study	:	Observation Study
Duration of time	:	1 Year
Categories of drug	:	Antineoplastic Agents

Mechanism of action Alectinib:- Anaplastic lymphoma kinase (ALK) and the RET proto-oncogene are two receptor tyrosine kinase enzymes that the drug potently and specifically suppresses [32]. Similar anti-ALK action is shown in the active metabolite M4. Apoptosis (cell death) of cancer cells is subsequently induced by ALK inhibition, which also inhibits other cell signalling pathways such as STAT3 and the PI3K/AKT/mTOR pathway [34, 35].

Mechanism of action Daunorubicin:- Similar to daunorubicin, it interacts with DNA by intercalating and preventing the formation of large molecules [36]. Hemoglobin's ability to relax super coils in DNA for transcription is hampered by this. After breaking the DNA chain to allow for replication, daunorubicin stabilises the haemoglobin complex, preventing the DNA double helix from being resealed and putting an end to the replication process. DAU intercalates when it binds to DNA, with its DAU residue pointing in the direction of the minor groove [37, 38]. The configuration that it like the most is two adjacent G/C base pairs that are surrounded on the 5' side by an A/T base pair. Crystallography demonstrates that DAU causes additional conformational disruptions of nearby and second-neighbor base pairs, including a local unwinding angle of 8°. It may also cause his tone to be ejected from

Result:-

Creatinine and BUN Level :- Creatininee in the group was increased significantly compared with that in the control group (2.05±0.83 mg/dL) and Alectinib group (2.35±0.95 mg/dL). Administration of was observed to prevent this increase when administered with Daunorubicin group (1.86±0.76)mg/dL.

Haematological Study:- Red blood cells (RBC), haemoglobin, and enhanced red cell distribution width (RDW) were all significantly lower in all AC-treated groups at the intermediate time point compared to the basal time point and control group. However, while these parameters reverted to normal levels in groups ALECTINIB and DAU at the end of the induction period, they remained abnormal or even got worse in the DAU3 group. White blood cell (WBC) count was considerably impacted by the DAU protocol at the intermediate time point in comparison to values and those of the alectinib group, which is consistent with higher haematological toxicity; however, these levels rebounded to virtually normal at the end of the induction phase.

Biochemical parameters:- Daunorubicin was administered repeatedly, and this generated considerable alterations in various indicators, especially those that were related to creatinine, BUN, SGPT, and SGOT. The same metrics, as well as cholesterol, atrium, potassium, and phosphates, were all significantly affected by alectinib. More of these alterations were visible in the alectinib group compared to the daunorubicin group. Both groups experienced a significant rise in CRP, which indicated the existence of inflammatory processes. In contrast to the considerable increase in the control group, both anthracyclines dramatically reduced serum iron levels.

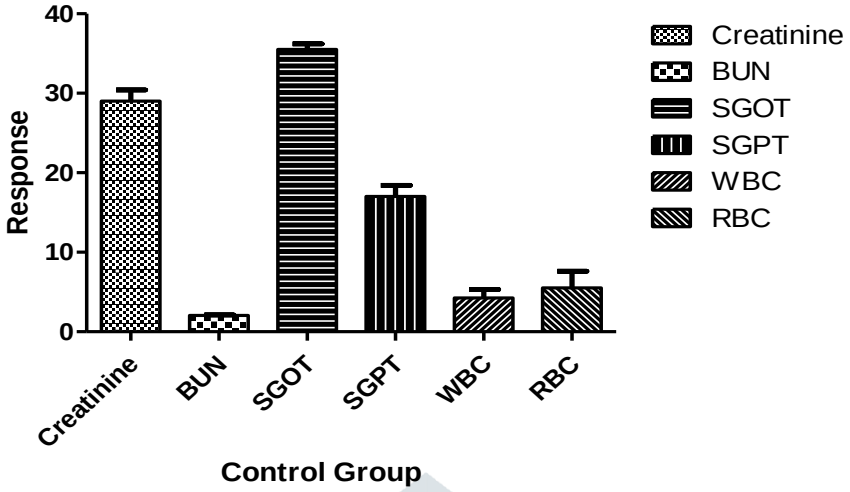
Table no.1

GROUP	BUN mg/dl	Creatinine mg/dl	SGPT U/L	SGOT U/L
CONTROL	29±11.8	2.05±0.83	35.5±0.28	17±6.9
ALECTINIB	34±13.8	2.35±0.95	35±1.6	22±8.9
DAUNORUBICIN	32±13.06	1.86±0.76	44±1.6	46±18.7

Table no. 2

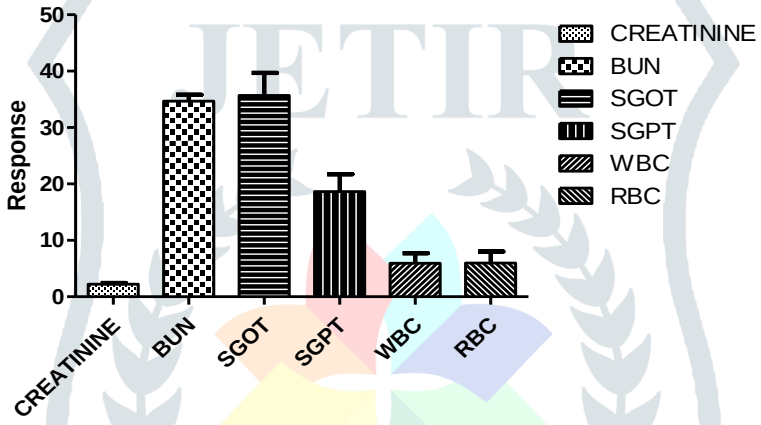
GROUP	BUM mg/dl	Creatinine mg/dl	SGPT U/L	SGOT U/L	WBC uL	RBC uL
Control	29±11.83	2.05±.0.83	35.5±14.49	17±6.94	4.5±1.73	5.5±2.24
Alectinib	34.66±14.15	2.23±0.91	35.66±14.56	18.66±7.62	5.2±2.12	5.96±2.43
Daunorubicin	31.33±12.79	1.83±0.74	46±18.78	21.33±8.70	4.76±1.94	7.4±3.04

GRAPH: 1



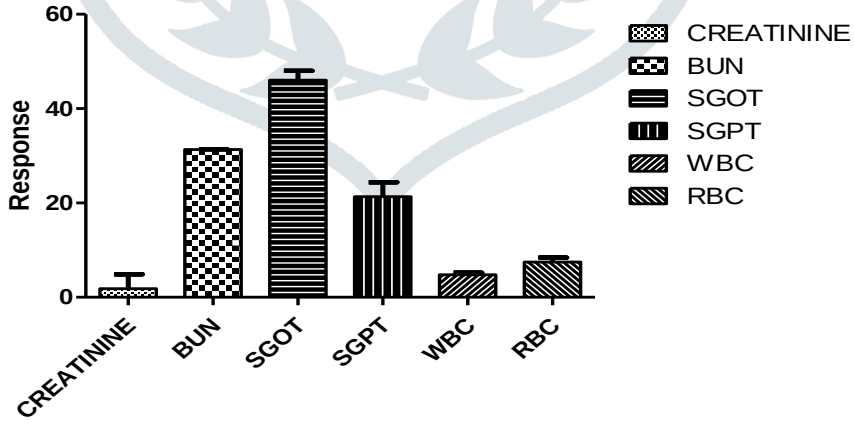
Control Group

GRAPH 2



ALECTINIB GROUP

GRAPH 3



DAUNORUBICIN GROUP

6. Discussion:- To examine the chronic harmful effects of alectinib and daunorubicin in our investigation, rabbits received both drugs on the same schedule of dosing. Anthracycline dosages given to animals were similar to those given to humans.When daunorubicin or alectinib are given to rabbits on a regular basis, the usual changes result. In order to induce dose-dependent cumulative haematology in rabbits, both drugs have been utilised. This rabbit model is primarily used for the testing of possible hemology protecting agents. The daunorubicin group's slight and insignificant increase in body weight as well as the level of early mortality brought on by liver and partially also by renal toxicity was analogous to our prior observations. On the other

hand, all of the alectinib-treated rabbits exhibited significant emaciation and all of them passed away before their time. Similar findings regarding

Conclusion:- The anthracycline anticancer medications are administered to additional individuals at the highest doses. Alectinib with daunorubicin administration's effects on body weight and physical condition on the value of anticancer drugs. Alectinib, daunorubicin, and other types of drug delivery systems should be evaluated at various doses. It is also important to contrast intratumoral and subperitoneal approaches.

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