ABSTRACT & AIM OF THE WORK

TITLE NAME: Biological Studies on the Effect of Bone Marrow Transplantation and Low dose of Gamma Irradiation on Rat Liver Regeneration.

Key Words: Carbon tetrachloride- Low dose gamma radiation- Bone marrow cells- Fibrosis- DNA ploidy- Liver- Rat.

Objective: Light microscopical, ultrastructural, DNA ploidy, biochemical and cytogenetical assessment were conducted to allocate the role of bone marrow cells transplantation and chronic low dose gamma irradiation of rats against carbon tetrachloride induced liver fibrosis.

In recent years, bone marrow transplantation has been widely investigated as potentially useful protective agent in many pathological changes. Liver is the hardest working organ in the human body; it is usually used as a highly regenerating organ when induced by toxins. The aim of the present study was to evaluate structural and biochemical effect of CCl_4, as a common toxin, on highly proliferating organ (the liver). Also this work discusses the protective action of bone marrow cells transplantation and chronic low dose gamma radiation against the liver injury induced by CCl_4.

Experimental design and methods: Adult male albino rats were classified into six groups. The first group was normal control; the second one was bone marrow cells administrated (1 ml/ Kg), the third group was carbon tetrachloride administrated (1 ml/kg body weight, twice a week) for four and eight weeks, the fourth group was irradiated (0.5 Gy, twice a week) for four and eight weeks, the fifth group was irradiated and carbon tetrachloride administrated (0.5 Gy and 1 ml/kg body weight of CCl_4, twice a week) for four and eight weeks, the sixth group was bone marrow administrated group in which 1ml of bone marrow cells

was injected (as one dose at the fourth week) to all for mentioned groups, then continue the process of irradiation and CCl_4 injection for another four weeks. Histopathological, ultrastructural, DNA ploidy, biochemical and cytogenetic studies assessments were estimated.

Results: CCl_4 treated rats showed many structural changes start from fibrosis and malformation of the nucleus to complete death. Biochemical and cytogenetic studies were performed to assess these results where carbon tetrachloride administration showed an increase in ALT, AST, TBARS and hydroxyproline content with a decrease in the total protein and GSH levels. It also showed an increase in the chromosomal aberrations with a decrease in the mitotic activity of the bone marrow cells. In addition, quantitative DNA image analysis showed marked decrease in the DNA content post CCl_4 administration.

Bone marrow transplantation was found to ameliorate the pathological changes in all examined rat groups more than chronic low dose gamma irradiation where the hepatocytes showed a recovery process faster than that of chronic low dose gamma irradiation indicating its protective effect against liver injury.

Conclusion: On the light of the current results it could be concluded that chronic low dose gamma irradiation and/or bone marrow cells transplantation may enhance the process of rat liver regeneration following liver fibrosis induced by carbon tetrachloride administration.

Aim of the work

The liver is the most common target for toxic injury. Most chemicals are not biologically active but can be converted to toxic metabolites (metabolic activation). This conversion often involves the P_{450} mixed function oxidases located in the smooth endoplasmic reticulum, most prominently in the liver.

The current work was designated to investigate the effect of bone marrow cells (BMC) transplantation and/or chronic low dose (0.5 Gy) gamma irradiation on established rat liver fibrosis induced by carbon tetrachloride (hepatotoxin) administration.

The influence of bone marrow cells transplantation and/ or chronic low dose (0.5 Gy) gamma irradiation was assessed through investigating the following:

- Histopathological study.
- Ultrastructural study.
- DNA Cytometry.
- Biochemical study.
- Cytogenetic study.

The current results aimed to evaluate the fibrotic effect of carbon tetrachloride and in investigating the possible role of bone marrow cells transplantation and/or chronic low dose gamma irradiation as ameliorating agents against liver fibrosis.

1. Introduction

The liver disorders are a worldwide problem. Despite its frequent occurrence, high morbidity and high mortality, its medical management is currently in adequate, no therapy has successfully prevented the progression of hepatic diseases, even though newly developed drugs which have been used to treat chronic liver disorders these drugs have often side effects.

Chronic hepatic injury leading to fibrosis occurs in response to a variety of insults, including viral hepatitis, alcohol abuse, drugs, and metabolic diseases involving an overload of iron or copper, autoimmune diseases or congenital abnormalities **(Friedman, 2000 ; Pinzani *et al.*, 2001)**.

Carbon tetrachloride (CCl_4), a classic hepatotoxin, causes acute, reversible liver injury characterized by centrilobular necrosis, followed by hepatic regeneration and repair. This liver injury is attributed to inflammatory responses originating from CCl_4-derived free radical formation in the liver and concomitant activation of non parenchymal cells. Sustained hepatic inflammation provoked by long-term administration of CCl_4 was believed to induce hepatic fibrosis through ongoing hepatocytic necrosis and production of fibrogenic cytokines acting on fibroblasts, including activated hepatic stellate cells **(Parola and Robino, 2001)**.

Low doses of gamma radiation were found to stimulate various biological functions: anti-oxidative capacity, DNA repair capability and immune functions. Each of these functions may work in a suppressive manner in the process of carcinogenesis, which would be initiated with DNA damage induced directly by radiation or through reactive oxygen species production **(Sakai *et al.*, 2006)**.

According to **Yokoyama *et al.* (2006)** transplanted bone marrow cells can reduce carbon tetrachloride-induced liver fibrosis in rats, but low doses of gamma radiations can improve their liver regeneration; bone marrow cells can differentiate into a number of other types of cells including liver cells, which could help patients with liver cirrhosis and chronic liver failure. The present study clearly indicates that intravenous injection of bone marrow cells and low dose of gamma radiation exposure are responsible for the resolution of liver fibrosis induced by CCl_4 administration.