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İRİNOTECAN UYGULANAN RATLARDA DENEYSEL KARACİĞER REZEKSİYONU SONRASINDA GRANÜLOSİT KOLONİ STİMÜLE EDİCİ FAKTÖRÜN REJENERASYON ÜZERİNE ETKİLERİ

THE EFFECTS OF GRANULOCYTE COLONY STIMULATING FACTOR ON REGENERATION AFTER EXPERIMENTAL LIVER RESECTION IN IRINOTECAN ADMINISTERED RATS

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Keywords: Hepatectomy, granulocyte colony stimulating factor, irinotecan, liver regeneration

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ÖZ

Giriş: *Çeşitli nedenlerle gerçekleştirilen karaciğer rezeksiyonları sonrasında meydana gelen karaciğer rejenerasyonunun mekanizmalarının daha iyi anlaşılması gerekmektedir. Bu çalışmada granülosit koloni uyarıcı faktörün karaciğer rejenerasyonu üzerindeki etkisini değerlendirmeyi amaçladık.*

Gereç ve Yöntem: *Elli adet Sprague-Dawley albino rat 5 gruba ayrıldı.Grup A: Sham grubu (n: 10), Grup B: Karaciğer rezeksiyon grubu (n: 10), Grup C: G-CSF + Karaciğer rezeksiyon grubu (n: 10), Grup D: İrinotekan + Karaciğer rezeksiyon grubu (n: 10), Grup E: İrinotekan + G-CSF + Karaciğer rezeksiyon grubu (n: 10). Karaciğer sadece grup A'daki sıçanlarda açığa çıkarıldı. Grup B'de tüm sıçanlara laparotomi ve ardından karaciğer rezeksiyonu yapıldı. Grup C'de laparotomi sonrası karaciğer rezeksiyonu yapıldı ve 1 milyon ünite tek doz G-CSF intraperitoneal olarak uygulandı. Grup D'de laparotomi sonrası karaciğer rezeksiyonu yapıldı ve sıçanlara ameliyattan 7 gün önce 300 mg / m^2 irinotekan uygulandı. Grup E'ye operasyondan 7 gün önce 300 mg / m^2 irinotekan uygulandı; laparotomi sonrası karaciğer rezeksiyonu yapıldı ve aynı anda 1 milyon ünite G-CSF verildi. Çalışmada kan örneklerinde AST, ALT ve MDA değerlendirildi. Karaciğer rejenerasyonuna yönelik PCNA immünohistokimyasal olarak, mitotik indeks ise rutin H&E yöntemiyle belirlendi. Ayrıca dokuda MDA düzeyinin belirlenmesi için biyokimyasal inceleme yapıldı*

Bulgular: *Kan AST ve ALT düzeyleri gruplar arasında anlamlı farklılık gösterirken doku/serum MDA düzeyleri gruplar arasında anlamlı farklılık göstermedi. Mitotik indeks ve PCNA indeksi oranları karşılaştırılmış ve gruplar arasında anlamlı fark bulunmuştur. Karaciğerdeki yağ ve fibroz oranları, gruplar arasında benzerdi. Karaciğer rejenerasyonu, grup E ile grup C arasında istatistiksel olarak benzer iken, grup E'de karaciğer fibrozu ve adipozite anlamlı olarak artmıştır*

Sonuç: *Granülosit koloni uyarıcı faktör, karaciğer rejenerasyonunu artırdı ancak fibroz ve yağlanma üzerinde anlamlı bir etkiye sahip değildi.*

SUMMARY

Introduction: *The mechanisms of liver regeneration that occur after liver resections performed for various reasons should be better understood. In this study aim to evaluate the effect of granulocyte colony stimulating factor on liver regeneration.*

Material and Method*: Fifty Sprague-Dawley albino rats were divided into 5 groups. Group A: Sham group (n: 10), Group B: Liver resection group (n: 10), Group C: G-CSF + Liver resection group (n: 10), Group D: Irinotecan + Liver resection group (n: 10), Group E: Irinotecan + G-CSF + Liver resection group (n: 10). The liver was only exposed in rats in group A. In group B, all rats underwent laparotomy followed by liver resection. In group C, liver resection was performed following laparotomy, and 1 million units of a single dose of G-CSF was administered intraperitoneally. In group D, liver resection was performed after laparotomy, and the rats were administered 300 mg/m^2 irinotecan 7 days preoperatively. In group E, 300 mg/m^2 irinotecan was administered 7 days before the operation; after the laparotomy, liver resection was performed, and 1 million units of G-CSF was given simultaneously. In the study, AST, ALT and MDA were evaluated in blood samples. PCNA for liver regeneration was determined immunohistochemically and mitotic index was determined by routine H&E method. In addition, biochemical examination was performed to determine the MDA level in the tissue.*

Results: *Blood AST and ALT levels showed significant difference between the groups but tissue/serum MDA levels showed no significant difference between the groups. The ratio of mitotic index and PCNA index were compared, and a significant difference was found between the groups. Liver regeneration was statistically significant in group E compared to that of group D. Fatty and fibrosis rates in the liver were similar between the groups. Liver regeneration was statistically similar between group E and group C, whereas liver fibrosis and adiposity were significantly increased in group E.*

Conclusion*: Granulocyte colony stimulating factor increased liver regeneration but had no significant effect on fibrosis and fattening.*

INTRODUCTION

Liver resection is the treatment choice for various primary and secondary liver tumors (1). The number of centers where liver operations are performed and the number of operations are increasing. It is necessary to understand the mechanisms of ischemic injury during surgical treatment and liver regeneration after resection for various reasons. When the liver reaches adult size, it stops growing. However, after liver tissue injuries, diseases such as viral hepatitis and cirrhosis, toxic events, or surgical removal of a part of the liver, rapid compensatory growth occurs, and this growth continues until the liver reaches adult dimensions. Functional liver healing is completed within two weeks after the loss of 2/3 of the liver. Many growth factors and cytokines play a role in this regeneration mechanism of the liver. Several studies conducted in recent years have investigated the regenerative ability and pathophysiological mechanisms of the liver and the effects of multiple agents on liver regeneration following partial hepatectomy.

Liver regeneration is an organized response that includes changes in gene expression, growth factor production and liver morphological structure (2). The mechanism and kinetics of liver regeneration as well as potential regenerative factors are continuously investigated. Several attempts were made to increase functional capacity after liver resection (3-5).

G-CSF is a hematopoietic growth factor. G-CSF receptors are expressed not only by hematopoietic cells but also nonhematopoietic cells, including hepatocytes and vascular endothelial cells. Although G-CSF has known effects on facilitating liver regeneration, the exact mechanism of its action is unclear (4). This report presents the effect of granulocyte colony stimulating factor on liver regeneration.

MATERIALS AND METHOD

This experimental study was conducted in the Osmangazi University Medical Faculty T.İ.C.A.M. (Medical and Surgical Research Center) laboratory. The study protocol was approved by the local ethics committee of the same center (date 110 / 13.5.2009). For this study, 50 Sprague-Dawley albino rats were used. The rats were 230 ± 30 grams in weight and of both sexes. All experimental animals were obtained from T.İ.C.A.M. and were kept in automatically adjusted rooms with controlled temperature (22 ±

2 °C) and humidity (45-50%) with 12:12 light: dark illumination during the experiment. During this adaptation process, all rats were kept in transparent polycarbonate cages and were provided standard rat feed and tap water.

Group A: Sham group (n: 10) randomly chosen from the experimental animals

Group B: Liver resection group (n: 10)

Group C: G-CSF + Liver resection group (n: 10)

Group D: Irinotecan + Liver resection group (n: 10)

Group E: Irinotecan + G-CSF + Liver resection group (n: 10)

After 8 hours of fasting, all rats underwent subcutaneous 50 mg/kg sodium pentothal anesthesia. After anesthesia, the rats were placed in the supine position, and a median laparotomy incision was performed with 10% povidone iodine. The liver was only exposed in rats in group A. In group B, all rats underwent laparotomy followed by liver resection. In group C, liver resection was performed following laparotomy, and 1 million units of a single dose of G-CSF was administered intraperitoneally. In group D, liver resection was performed after laparotomy, and the rats were administered 300 mg/m^2 irinotecan 7 days preoperatively. In group E, 300 mg/m^2 irinotecan was administered 7 days before the operation; after laparotomy, liver resection was performed, and 1 million units of G-CSF were given simultaneously.

After the procedures were completed for each described group, the rats were placed in individual cages. The rats were fed standard rat food and tap water 12 hours after the operation. All rats were anesthetized on the 3rd postoperative day, and the residual livers were removed. Intracardiac blood samples were taken. The determination of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and malondialdehyde (MDA) concentrations in the blood was performed in the Biochemistry department. The wet weight of the removed livers was noted, and some of the liver tissues were fixed in neutral formalin. Proliferating cell nuclear antigen (PCNA) for liver regeneration was determined immunohistochemically, and the mitotic index was determined by the routine haematoxylin eosin (H&E) method in the Histology and Embryology Department. The level of MDA in the tissue was determined. In the Histology and Embryology Department, routine follow-up of the tissues fixed with neutral formalin was performed with a tissue tracking device after fixation. Serial sections of approximately 4 microns thick were taken from each of the tissues prepared with paraffin blocks. For general evaluation and mitotic index detection, H&E staining was performed in the sections, and PCNA immunohistochemical staining was used to evaluate regeneration. The mitotic index was calculated by the approximate number of cells in randomly selected fields at 40× magnification.

Biochemical Analysis

Serum yield: Blood samples were obtained by centrifugation at 1500 g for 15 minutes.

Obtaining tissue samples: Tissue samples taken during the experiment were washed three times with saline and stored at -20 °C until the tissues were homogenized in 0.15 M KCl buffer (1 g tissue + 9 ml buffer) and centrifuged at 500 rpm. The supernatant was used for analysis.

Determination of serum and tissue malondialdehyde (MDA) levels: MDA levels were determined manually based on the principle of measuring absorbance at 532 nm of the color generated by MDA in thiobarbituric acid in acid medium according to the method of Ohkaea et al. AST activities were determined by spectrophotometry using commercial kits. The results obtained from tissue measurements were calculated by normalizing to the tissue protein levels.

RESULTS

The mean liver weight was 8.6±0.4 for group A. After resection, the MLW decreased to 5.2±0.5, 8±0.1, 5.3±0.9 and 7.6±0.4 for groups B, C, D and E, respectively. A significant difference was observed in Group B (F=74.505; p<0,001) compared to that of Group C (G-CSF) and Group E (IRT+G-CSF).

For blood AST and ALT values, a significant difference was found between the groups. For tissue and serum MDA levels, no significant difference was found between the groups (Table 1).

Mitotic index

All groups were examined with hematoxylin and eosin staining. The ratio of mitotic hepatocytes to nonmitotic hepatocytes (mitotic index) was compared, and a significant difference was found between the groups ($\chi 2 = 33,99$; $p < 0.001$).

There was a significant difference in the decrease in mitotic index ($p < 0.001$) in the irinotecan group compared to that of groups A and B ($p < 0.001$). There was a significant difference in the increase in group E ($p < 0.001$). The mitotic index ratio was lower in group A than in the other groups. There was a difference between group C and group B ($P < 0.05$). The mitotic index ratio was higher in group C than in group B. There was a difference between group C and group D ($P < 0.001$). The mitotic index ratio in group C was higher than in group D. There was a difference between group C and group E ($P < 0.01$). The mitotic index ratio in group C was higher than in group E. There was no difference between groups D and B ($p > 0.05$). There was no difference between groups D and E ($p > 0.05$). There was no difference between groups E and B ($p > 0.05$).

PCNA index

When PCNA-stained liver sections of all groups were examined, the ratio of the number of PCNA (+) hepatocyte nuclei to PCNA (-) hepatocyte nuclei was compared with the PCNA index, a significant difference was found between the groups ($\chi 2 = 17.74$; $P < 0.01$) (Figure 1).

There was a statistically significant increase in the number of PCNA (+) cells in the PCNA index between group A and group B ($p < 0.05$), group C ($p < 0.01$) and group E ($p < 0.01$). The number of PCNA (+) cells in group A was less than that in the other groups. There was no difference between groups C and B ($p > 0.05$). There was a statistically significant difference between groups C and D ($p < 0.01$). The number of PCNA (+) cells in group C was higher than that in group D. There was no difference between groups C and E ($p > 0.05$). There was a difference between groups D and B ($p < 0.01$). In group D, the number of PCNA (+) cells was less than that in group B. There was a difference between groups D and E ($p < 0, 01$). The number of PCNA (+) cells in group D was less than that in group E. There was a difference between groups E and B ($p < 0.01$). In group E, the number of PCNA (+) cells was less than in group B.

Table 1. The results of mean liver weights and biochemical analysis in the groups.

	Group A	Group B	Group C	Group D	Group E	p
Mean Liver Weight	8.6±0,4	5.2±0,5	8±0,1	5.3±0,9	7.6±0,4	p<0,001
AST levels	289.8±137.5	1130.5±405.9	1279.8±724.2	800.5±565.6	599.9±355.7	p<0,001
ALT levels	151.5±60.3	508.5±230.5	499.2±285.83	473.7±478.2	272.0±201.0	p<0,001
Serum MDA levels (nmol/g)	3.8±1.3	3.8±.0.4	4.5±1.7	3.2±0.6	3.5±0.5	P>0.5
Liver tissue MDA levels (nmol/g)	0.7±0.4	0.6±0.2	1.0567±0.4	1.2±1.1	1.2±0.8	P>0.5

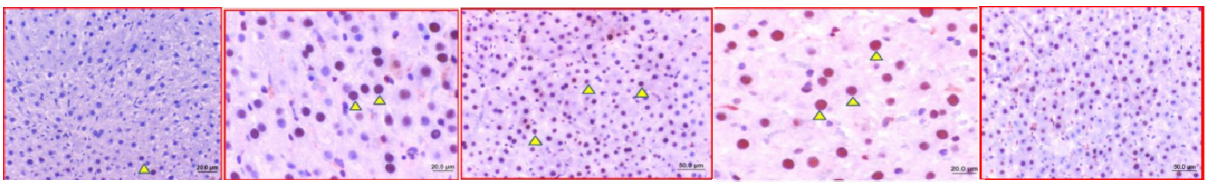

Figure 1.PCNA (+) hepatocyte nuclei for group A-E

DISCUSSION

In the experimental model, liver tissue was not exposed to prolonged ischemia. Therefore, similar findings between the groups were not considered unexpected. In our study, a statistically significant increase was observed in the PCNA and mitotic indexes in group E compared to those in group D. Similarly, only a statistically significant difference was observed between groups D and C. According to these results, G-CSF will have positive effects on regeneration in patients who undergo liver resection after irinotecan.

In this study, hydropic degeneration was determined in some hepatocytes in liver sections from group E. In addition, dilatation and congestion were observed in sinusoids located between hepatic cords. The presence of the same histological condition in group D revealed that G-CSF had no positive effects on hepatocyte fat, degeneration and fibrosis. This result is in parallel with the results of similar studies (16-19).

The liver has a unique property of regeneration capacity. This is an early and fast response that is usually completed shortly after trauma. Fast functional liver regeneration after any form of injury has a high clinical impact on the subject's outcomes. Several autologous or allogeneic cell therapies have been used to augment liver repair (17).

In the present study, we used a 70% hepatectomy model. Higgins and Anderson's 2/3 hepatectomy model is a well-established model for experimental studies (6). In rodents, 60%-70% of liver resection almost always results in complete regeneration and high survival rates. If the remnant liver is less than 30% or less than 0.08% of body weight, this leads to small-for-size liver remnant syndrome, which leads to marked regeneration impairment, acute liver failure and increased morbidity and mortality (5).

Irinotecan hydrochloride is a cytotoxic chemotherapy agent. Its active metabolite is SN-38. Irinotecan inhibits DNA topoisomerase 1 and is currently used for the treatment of various solid tumors. It is generally regarde as a safe chemotherapy agent with limited side effects, such as leukopenia and intestinal toxicity (3,16).

Within 24 hours of partial hepatectomy, active cell replication begins and continues until the initial weight of the organ is reached. Although various methods can be used to evaluate liver function after I/R injury due to liver surgery, the most widely accepted and used is the determination of AST, ALT and MDA activity. It is known that the activity of these enzymes increases in liver damage. Yabe et al. suggested that the levels of ALT, AST and MDA in the liver increased as a result of ischemia reperfusion injuries (7,20). In our study, an increase was observed in the AST and ALT values in the G-CSF group; however, no statistically significant difference was observed between these groups. There was no statistically significant difference between the mean values of MDA in blood and tissue samples. In the experimental model, liver tissue was not exposed to prolonged ischemia. Therefore, similar results between the groups were not considered unexpected. In response to liver damage, silent hepatocytes begin to differentiate quickly. If lethal damage occurs in the liver after 65-70% resection, the hepatocytes begin to grow to compensate for the lost cells. H&E staining showed radial hepatic cords and open sinusoids in the control group in a study of 50% partial hepatectomy and nonsurgical mice.

In the surgical group, severe acidophilic necrosis was observed in liver cells on days 1-3 post-PH, and the sizes of most hepatocyte nuclei increased. There were vesicular bodies and stromal inflammatory cell infiltration. On day 25, evidence of liver damage was reduced. However, the presence of large nuclei, indicative of cell division, persisted (8). In our study, hydropic degeneration of hepatocytes was quite common in the group treated with PH similar to other studies, and in some areas with sinusoidal dilatation and congestion, PMNL (polymorphic nuclear leukocyte) and MNL (mononuclear leukocyte) infiltration was observed. In addition, the prevalence of mitosis in hepatocytes was remarkable. Non-alcoholic fatty liver disease (NAFLD) is characterized by various degrees of inflammation, fibrosis and necrosis and lipid accumulation in hepatocytes. It has been shown that the complication rate is increased in patients with hepatectomy steatosis. These steatohepatic changes were found to be associated with preoperative chemotherapy (9). Chemotherapy-related steatohepatitis (CASH) is a common

finding in liver resection specimens after administration of irinotecan-induced regimens (10). In our study, partial hepatectomy (PH) and a single dose of irinotecan were administered. This type of study in rats was not available in the literature. In our study, the prevalence of micro- and macrovesicular vacuolization in hepatocytes was determined in liver sections of this group. In addition, dilatation and congestion were observed in sinusoids, which are among the hepatic conditions. PMNL infiltration was seen in some areas. In our study, micro and macrovesiculation seen in the group treated with PH and irinotecan were not observed in the group treated with only PH. The effects are thought to be caused by irinotecan (16,21).

G-CSF improves proliferation and mobilization of the bone marrow progenitor cell population (11,17-20). It has anti-inflammatory and anti-infectious effects. Clinical information has shown that administration of G-CSF in humans provides hepatic support after acute liver failure and major surgical interventions; however, the exact mechanism of G-CSF remains unclear. In one study, the PCNA index was found to be significantly higher in the G-CSF-treated group before 60% hepatectomy compared to that of the non-G-CSF-treated group on the 2nd and 3rd postoperative days. In the same groups, the mitotic index increased significantly on postoperative day 2. The liver is the target organ of some cytokines, and some cytokines have been shown to affect hepatocyte proliferation. Some drugs and factors increase hepatocyte proliferation and have a positive effect on postoperative liver failure. G-CSF is one of these drugs. G-CSF is a cytokine that regulates various neutrophilic functions (12). G-CSF receptors are also expressed in nonhematopoietic cells such as hepatocytes and vascular endothelial cells. In this study, hepatic sinusoidal diameter increased in the G-CSF + partial hepatectomy and only partial hepatectomy groups. G-CSF was administered preoperatively for 5 days.

With the use of different available forms, Theocharis et al. demonstrated that liver regeneration occurred earlier when compared with that of simple hepatectomy (6). In three experimental groups, Sidler et al. demonstrated that G-CSF increased sinusoidal diameter and increased hepatic blood flow (5). Sinusoidal blood flow was increased in both groups, and hypertrophy was seen in hepatocytes. The effect of G-CSF on regeneration is thought to be mediated by a direct effect on hepatocytes, by indirect signaling by nonparenchymal cells or by extrahepatic mediators (e.g., increased circulating levels of G-CSF-mediated hepatocyte growth factors) (5). In our study, sinusoidal dilatation was seen in the G-CSF and PH group. Hepatic necrosis areas, hypertrophy of hepatocytes, and mitotic figures increased in this group. Theocharis et al. showed that single-dose G-CSF administration increased hepatocyte proliferation in rats with partial hepatectomy and fulminant hepatic insufficiency (13). G-CSF increases the first peak of hepatocyte proliferation after PH in rats irrespective of the time of administration. Concomitant administration of PH with G-CSF not only increases rat hepatocyte proliferation capacity but also displaces the first peak of hepatocyte DNA biosynthesis at the earliest time. G-CSF administration in a rat model (such as cadmium intoxication) that reduced hepatocyte regeneration after PH improved the suppressed hepatocyte regeneration capacity. In another study, it was shown that the application of G-CSF increases the repair mechanisms that trigger hepatocyte proliferation caused by toxic damage induced by D-galactosamine in rats. When the same dose of G-CSF is administered in rats with PH, hepatocyte proliferation increases and the regeneration peak time changes at 20-24 hours after hepatectomy (6).

G-CSF administration did not affect DNA biosynthesis or thymidine kinase activity in healthy nonhepatectomized or other rats. Mitotic activity did not increase. This finding supports the hypothesis that G-CSF and liver growth factors affect mitotic activity in silent hepatocytes with low sensitivity (6). Yao et al. studied the mitotic index and PCNA staining index of a 70% partial hepatectomy group. The remaining liver reached its original weight at 7-10 days in rats who underwent 70% partial hepatectomy (14). In a study by Hamada et al., the PCNA index peaked at 24 and 36 hours after 2/3 hepatectomy (15). In our study, the PH + irinotecan + G-CSF group showed hydropic degeneration of some hepatocytes in the liver sections. In addition, dilatation and congestion were observed in

sinusoids located between hepatic cords. In some areas, PMNL infiltration was observed. Irinotecan damage to hepatocytes was not completely prevented, but mitosis increased similar to that of group C. In the literature, there have been no study in which irinotecan and G-CSF were given together. In our study, a statistically significant difference was observed in group E compared to that of group D in terms of PCNA and mitotic index. Similarly, a statistically significant difference was observed only between groups D and C. These results were consistent with the literature.

In our study, a single dose of irinotecan was applied together with partial hepatectomy (PH). In our study, the prevalence of micro and macrovesicular vacuolization in hepatocytes in liver sections belonging to this group was determined. In addition, dilatation and congestion were observed in the sinusoids located between the hepatic chondons. PMNL infiltration was seen in some areas. In our study, the micro and macrovesiculation seen in the PH and irinotecan group was not seen in the PH group only. It can be thought that irinotecan caused the findings here.

In our study, hydropic degenerations were determined in some hepatocytes in the liver sections of the PH + irinotecan + GCSF group. In addition, dilatation and congestion were observed in the sinusoids located between the hepatic cords. PMNL infiltration was observed in some areas. It was observed that the damage caused by irinotecan in hepatocytes could not be completely prevented, but mitosis increased similarly to the GCSF group. There is no study in the literature in which irinotecan and GCSF were given together. In our study, a statistically significant difference was observed in the PH+irinotecan+GCSF group compared to the PH+irinotecan group in terms of PCNA and Mitotic index. Similarly, a statistically significant difference was observed between only the irinotecan group and only the GCSF group. These results were followed similarly to the literature results in which they were compared (16-22).

In our study, a statistically significant increase was observed in the PH + irinotecan + GCSF group compared to the PH + irinotecan group according to PCNA and Mitotic index calculations. Similarly, a statistically significant difference was observed between only the irinotecan group and only the GCSF group. According to these results, it was concluded that GCSF would have positive effects on regeneration in patients who underwent liver resection after irinotecan (16,18,20).

The main limitation of this study is that the sex difference could not be examined. There are numerous publication indicating sex related differences in the liver response to various factor (23,24). There is increasing amount of evidence for sex variation in drug efficiency and toxicity profiles. Females are more susceptible than males to acute liver injury. In general, this is attributed to sex differences at a physiological level as well as differences in pharmacokinetics and pharmacodynamics, but neither of these can give a sufficient explanation for the diverse responses to xenobiotics (23,24). Existing data are mainly based on animal models and limited data exist on in vitro sex differences relevant to humans. To date, male and female human hepatocytes have not yet been compared in terms of their responses to hepatotoxic drugs.

CONCLUSIONS

Further studies are needed to understand the pathophysiological and macroscopic damage after liver resection in patients receiving irinotecan and to better understand the mechanisms of G-CSF in liver regeneration.

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