Impact of Treatment with Imatinib on Renal Histology in Albino Rats

Luma Ibrahim Khalel Al-Allaf, Hafidh Al-Ashoo *

Abstract

**Background:** Targeted small molecule drugs have revolutionized treatment of chronic myelogenous leukemia (CML) over the last decade. however, their use has been found to be associated with serious toxic effects on a number of vital organs including the kidneys.

**Objectives:** This study aims to determine the histological changes of the kidney of rats after administration of a dose of 75mg/kg/once/day of Imatinib mesylate for one month in comparison to control ones.

**Study setting and design:** This experimental study was conducted on 16 male Albino rats purchased from Animal Houses of Veterinary College, University of Mosul, Mosul, Northern Iraq.

**Methods:** In this study a group of eight rats (40-45 days) were administered orally daily dose of 75mg/Kg/30 days of imatinib mesylate (Glivec®; Novartis). Another group of 8 rats (40-45 days) were administered distilled water (D.W). Kidneys tissues from each rat were obtained. The tissues were embedded in paraffin and stained with hematoxylin-eosin, periodic acid schiff +Hematoxylin stain, Toluidin blue, and Masson’s Trichrome.

**Results:** Rats treated with 75mg/kg/once/day of imatinib for 30 days showed different histological changes in glomeruli and some parts of the urinary tubules in comparison with controls. The most evident features are increase in Bowman's space, presence of lobulated or segmented glomeruli, shrunken glomeruli, dilated tubules with sloughed epithelium, and cloudy degeneration. Congested glomerular capillaries are also noticed sometimes in these sections with decreased Bowman's space. Dramatic renal injury in these rats was represented with tubular cell swelling, loss of brush border of proximal convoluted tubules as well as presence of cloudy degeneration of tubules. In addition, there was a focal accumulation of inflammatory cells of early inflammation that infiltrate between the tubules at the cortical and corticomedullary portion and early fibrosis is noticed. Sections obtained from rats treated with imatinib exhibit dilatation and hyperemia in the intertubular cortical or juxtamedullary blood vessels with appearance of structureless esinophilic area of necrosis. In addition, dilated tubules with accumulation of eosinophilic homogenous material in tubular lumen were noticed. The interstitial tissue showed area of hypercellularity, interstitial oedema and infiltration of mononuclear inflammatory cells (lymphocytes) which tend to be concentrated around the tubules in the cortical and medullary zones.

**Conclusion:** Imatinib has adverse effects on the renal histology and results in alterations in the renal cortex glomerular cells or tubular, which could play an important role in renal dysfunction. A clinical collaboration between oncologists and nephrologists could be useful with the objective to optimize the management of tyrosine kinase inhibitors.

**Keywords:** Imatinib mesylate, chronic myelogenous leukemia, nephrotoxicity, albino rats.

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**Introduction**

Targeted small molecule drugs have revolutionized treatment of CML over the last decade. However, their use has been found to be associated with serious toxic effects on a number of vital organs including the kidneys (1,2).

Chronic myelogenous leukemia (CML) is a myelo-proliferative disorder characterized by the presence of translocation t(9;22)(q34;q11) which generates the Philadelphia (Ph+) chromosome and the associated fusion gene (Abelson murine leukemia-break point cluster region ) (BCR-ABL) (3), which has deregulated tyrosine kinase activity and leads to increased cellular proliferation, resistance to apoptosis and genetic instability and it is at the center of CML pathogenesis (4). CML, once considered a fatal disease, is now essentially a chronic disorder, and most patients can enjoy long-term survival. This history of success has been the result of development of TKIs, compounds which suppress the abnormal tyrosine kinase (TK) activity of the BCR-ABL protein (5,6).

Imatinib (Gleevec® or Glivec® Novartis, NJ), is a selective, rationally designed, c-KIT and Bcr-Abl tyrosine kinase inhibitor, approved for the treatment of chronic myelogenous leukemia (CML) (7), gastrointestinal stromal tumors (GIST) (8,9), and unresectable GIST (10).

Imatinib undergoes P450 mediated metabolism mainly via CYP3A4 and CYP3A5 which play a minor role in the bile and only around 5-12% is excreted unchanged in urine (17,18). The main adverse effects include severe neutropenia and thrombocytopenia, oedema, fluid retention, nausea, mild diarrhoea, skin rashes, arthralgia, myalgia, bone pain, acute renal failure and hepatotoxicity (19,20,21,22,23).

Renal dysfunction is often unrecognized by the treating physicians who usually base their diagnosis on serum creatinine levels which is not a sensitive estimator of renal function and may give the physician the wrong impression that the renal function is still normal (24). Therefore, the use of formulas to estimate the glomerular filtration rate (GFR) or other methods that measure GFR is crucial and should be carried out routinely (25). There is little data on the influence of imatinib especially on the kidneys’ histology.

The rat is one of the most widely used research animal particularly the urinary anatomy, histology, and physiology (26). The rat is also useful in assessment of toxicological insult to the urinary system. They are initially used for experimental purposes since the half of the nineteenth century. Several strains have been developed for studying several diseases (27,28,29).

This study aims to evaluate the histopathological changes that occur in kidneys of rats after treatment with low dose of imatinib mesylate (75mg/kg/once/day) for one month duration in comparison to the control ones.

**MATERIALS AND METHODS**

This experimental study was conducted on male Albino rats purchased from Animal Houses of Veterinary College, university of Mosul, Mosul, Northern Iraq. Throughout the investigations the rats were housed under controlled normal environmental laboratory conditions and animal facility. They were local breaded and put individually in Animal House.
Impact of Treatment with Imatinib... Luma Ibrahim Khalil Al-Allaf, Hafidh Al-Ashoo

plastic cages (30,31) and provided with free access of water ad libitum and pelleted d food (32). The experiments were performed during the light portion (33).

Experimental design and procedures
Mean bodyweight of all rats was 70-110 gm. The first experiment includes 40-45 days aged rats which were administered daily dose of 75mg/Kg of imatinib mesylate (Glivec® Novartis) purchased from IBN-SENA Teaching Hospital or bought from some private pharmacies and were dissolved in D.W and were administered orally by gavage with needle (24 G) for 30 days (n=8) with age matched control who administered D.W following the same protocol applied to imatinib group (n=8).

Imatinib doses selected were intended to be in the range of those used in clinical treatment regimens (34). (400-800 mg/d or 340-590 mg/m² based on a weight of 70 kg) dose surface area adjusted to body-weight, \( f \times \text{mg/kg} = \text{mg/m}^2 \), where \( f \) is a constant equal to 6.0 in rats (35). Each animal was observed for overt signs of toxicity. The animals were firmly restrained (the animal was grasped by the loose skin of the neck and back) to immobilize the head and maintained in an upright (vertical) position. The needle (24 G) was passed through the side of the mouth, followed the roof of the mouth, and advanced into the esophagus toward the stomach. After the needle was passed to the correct length, imatinib was injected (36).

Study termination procedures: Animals in each experiment were euthanized with ether (30,37). 24 h after the final dose was given.

Tissue and organs collection: Kidneys of rats from each experimental group were obtained using longitudinal thoracoabdominal incision. The Kidneys were excised and examined macroscopically.

Preparation of histological sections: Kidneys were fixed in 10% Neutral buffered formalin (38). The frozen embedded wax blocks (Merck, Germany) were sectioned at 3-5μ thickness using Reichert-Jung microtome (Austria) (39,40), and slides were stained with Harris hematoxylin-eosin (Scarla, Spain) for general renal structure, periodic acid schiff stain+H Harris hematoxylin (PAS+H) to demonstrate the glycogen deposition in these sections, Toluidin blue stain was used as routine stain for renal sections, while Masson’s Trichrome were used for detection of mitochondrial contents in sections. The evaluation was blinded to treatment and any data by an expert histopathologist (Prof. Dr. Al-Nuami’s WMT).

Histopathological analysis
Renal changes were graded as mild, moderate, or severe. Scores +, ++, and +++ are mild, moderate, and severe levels, revealing less than 25, 50, and 75% histopathological alterations of total fields examined, respectively (23).

Photography:
All sections were visualized in Bright field Olympus microscope (Japan). Photomicrographs of representative changes were taken using digital camera (Optika, Italy, HD 1080, resolution 8.0 Mega pixels) attached using plan apochromatic objectives. The magnifications of photomicrograph were indicated with the legends for the photograph.

RESULTS
At necropsy, no obvious gross tissue abnormalities were noted in the kidneys of any animal.

The renal section of control rat (with intake of D.W alone) showed normal architecture of renal glomeruli with intact Bowman’s capsule. Brush bordered cuboidal epithelium lining the
proximal convoluted tubules. Simple cuboidal epithelium lining the distal convoluted tubules and normal medullary renal tubules (Figures 1a&b).

Rats treated with 75mg/kg /once/day of imatinib for 30 days showed different histological changes in glomeruli and some parts of the urinary tubules in comparison with controls. The most evident features are increase in Bowman's space, presence of lobulated or segmented glomeruli, shrinkage of glomeruli, dilated tubules with sloughed epithelium, and cloudy degeneration (Figure 2). Congested glomerular capillaries are also noticed sometimes in these sections with decreased Bowman's space (Figure 2). Dramatic renal injury in these rats was represented with tubular cell swelling, loss of brush border of proximal convoluted tubules as well as presence of cloudy degeneration of tubules.

In addition, there was a focal accumulation of inflammatory cells of early inflammation that infiltrate between the tubules at the cortical and corticomedullary portion (Figure 3). While early fibrosis is noticed in Figure 4. Sections obtained from rats treated with imatinib exhibit dilatation and hyperemia in the intertubular cortical or juxtamedullary blood vessels (Figures 5, 6), with appearance of structureless esinophilic area of necrosis as shown in Figure 5. In addition, dilated tubules with accumulation of esinophilic homogenous material in tubular lumen were noticed in Figure 7.

The microscopic observations in Figure 7 showed hyperemic vessels, congestion and dilatation of vessel, between the degenerated renal tubules at the corticomedullary portion. Dilated tubules with flattened epithelium, presence of sloughed cells in their lumina and extravasated RBC were revealed in Figure (8).

While Figure (9) showed sections with thickening of blood vessel wall.

On the other hand, the interstitial tissue showed area of hypercellularity, interstitial oedema and infiltration of mononuclear inflammatory cells (lymphocytes) which tend to be concentrated around the tubules in the cortical and medullary zones (Figure 10).

The effect of imatinib on renal histology in study groups is shown in Table 1.

Sections which were obtained from the rats of the control group showed presence of a considerable amount of carbohydrates in the cytoplasm of kidney cells using PAS-technique, which gave a red or magenta colour (Figures 11a and 11b). The nuclei, however, appeared entirely PAS-negative staining, indicating absolute lack of carbohydrates.

Treating rats with imatinib, caused a decrease of total carbohydrates in the kidney cells (Figure 12).

Using Masson’s Trichrome stain Figure 13a&b showed the normal reaction of the renal cortex and medulla.

Sections obtained from rats treated with imatinib revealed increase in the reaction to Masson’s Trichrome stain with decrease in the mitochondrial contents compared to that of control rats (Figure 14).

Effect of imatinib on the reaction of the renal sections of different groups to PAS is shown in Table 2.

**DISCUSSION**

Tyrosine kinase inhibitors are not entirely BCR–ABL1-specific, and this lack of specificity could account for the off-target effects of these drugs (25,41). It has been reported that these adverse events are off-target effects that are detrimental to the patient (42).

The present study indicated that
administration with 75mg/kg of imatinib induced various histopathological alterations in the renal sections of rats. These findings are consistent with those of others (43,44), where they classified the drug-induced renal disease into 3 main areas- glomerular injury, vascular injury and tubule-interstitial changes. Observations of previous studies revealed that lesions in these areas are frequently seen together as shown in this study (43,45).

This work revealed that imatinib has an influence on renal histology in these different areas with approximately similar degrees. These observations were similar to that of others (41), who reported that the renal toxicity of targeted therapies are most often due to structural damages of the nephron. In addition, several case reports showed that coincidently, with the start of treatment with imatinib, the patient develop acute renal failure (2,46,47), and acute tubular necrosis as being observed on histopathology (2).

However, Nassar et al., showed that there are very minor renal changes were observed, which may be anticipated since they used a single oral dose of 100 mg/kg of imatinib (39).

Light microscopic observations in the current study showed that repeated administration of imatinib at 75mg/kg induced several lesions as the appearance of glomerular swelling, periglomerular fibrosis, peritubular fibrosis, accumulation of mononuclear inflammatory cells in renal cortex and medulla, interstitial oedema and necrosis. Marcolina et al. revealed that the long-term treatment of imatinib may cause a clinically relevant decrease in the estimated glomerular filtration rate- GFR (25). However that is consistent with those of others, who treated a group of mice with a single dose of 100mg of imatinib (39). Padmini and Kumar reported that these findings reflect the severity of renal injury (48).

In addition, Alwin and Arthur reported that sloughed epithelial cells, cell debris and casts formation are a frequent finding of drug-induced renal injury (43).

The exact mechanism of chemotherapy-induced nephrotoxicity is not yet completely understood (21,49,23,50). Some authors suggested that this renal adverse effect may be caused by two possible mechanisms: the first is tumor lysis syndrome, with precipitation and deposition of uric acid in the renal tubules, and the second is the toxic tubular damage (25). Tubular cells are susceptible to the toxic effects of drugs, as they have a role in concentrating and reabsorbing the glomerular filtrate, what exposes them to high levels of circulating toxins (51). In the case of imatinib, the toxic effect may be related to platelet-derived growth factor receptor (PDGFR) inhibition (52,22).

Platelet-derived growth factor b-chain (PDGF-b) expression has been reported in proximal tubules and mesangial and interstitial cells (25). It has been shown in animal models that PDGF-b/PDGFR axis plays an important role in renal tubular cell regeneration after acute tubular necrosis (52). So, by inhibiting PDGFR, imatinib may interfere in tubular repair mechanisms.

The cytokines and tyrosine kinase receptors inhibited by imatinib and other tyrosine kinase inhibitors are important regulators of the two main mechanism of tissue injury repair, regeneration, and fibrosis (53).

On the other hand, Marcolin et al., revealed that the introduction of imatinib therapy in nonclinical trial CML patients is associated with decrease in estimated GFR and potentially irreversible acute renal injury (25).

Recently, renal associated adverse effects (RAEs) associated with sunitinib (a second
The toxic effects to other organs as the heart and the liver may modulate blood supply to the kidney and alter xenobiotic detoxification processes, respectively, thus indirectly contributing to drug-induced nephropathy (25,56).

The results from a study of Hu et al.,2011(57) strongly suggest that imatinib induces cardiac dysfunction through disruption of autophagy and induction of ER stress, independent of c-Abl inhibition, while Saad et al., reported that the effect of imatinib on rat’s livers may be attributed to the increase in NO production (37). Imatinib induced cardiotoxicity might be attributed to imatinib- induced PDGF receptor and c-Abl blockade (37). Recently, Hassan and Yousif reported that imatinib induce oxidative stress and release of cytochrom C and activation of caspases and leading to apoptosis in cardiac tissue of male rabbits (56).

Research on the pathogenic mechanisms of imatinib-induced hepatotoxicity or renal toxicity suggests that toxicity may be related to the P450 mediated metabolic pathway or idiosyncratic reactions in susceptible individuals (5).

The mechanism of glomerular and tubular injury such as swelling of their lining epithelial cells starts as a decrease in O2 levels which causes a drop in aerobic respiration. Renal cells consume oxygen at a high rate and are highly dependent on aerobic metabolism for ATP production(21), the cells must rely more on glycolysis. Glycolysis leads to lactic acid builds up which causes the intracellular pH to drop. Persistent ischemia can lead to mitochondrial and lysosomal damage, and membrane damage (58).

Another prominent histopathological changes in imatinib exposed kidney is thickening and interruption of glomerular basement membrane, which may play a role in renal dysfunction and reflected the decreasing in the GFR(44,48).

Light microscopic investigations of the current study showed a prominent dilatation of the renal vessels .Authors considered that finding as one of the structural changes of kidneys(59). It has been suggested that excessive production of NO causes vasodilatation and hypotension leading to organ hypoperfusion, edema and organ dysfunction(31).

In the present investigation, many renal tubules of the rat kidneys showed marked degenerative lesions under the effect of imatinib. This is justifiable since the renal tubules are particularly sensitive to toxic influences, in part because they have high oxygen consumption and vulnerable enzyme systems (58). Also the tubules come in contact with toxic chemicals during their excretion and elimination by the kidneys (25). Such degenerative changes were markedly pronounced in the proximal convoluted tubules ,these findings are similar to that of Padmini and Kumar(48). In addition, disintegration of
brush border membrane was shown in the present study, which may be responsible for the observed renal dysfunction\(^{(44)}\). Damage to the brush border and leakage of alkaline phosphates (ALP) and gamma-glutamyl transferase (GGT) enzymes, which are associated with the brush border of the renal tubules, as a result of toxin binding to the brush border and considered as an early marker of toxic tubular insult.

The results showed that treated rats with imatinib caused a depletion of carbohydrates in the cytoplasm of renal tubules. This result was in correspondence with other studies reported by others\(^{(60)}\). Finally, the findings of an increase of connective tissue elements of the kidney are similar to that of others\(^{(59)}\).

**In conclusion:** Imatinib has adverse effects on the renal histology and results in alterations in the renal cortex glomerular cells or tubular, which could play an important role in renal dysfunction. A clinical collaboration between oncologists and nephrologists could be useful with the objective to optimize the management of tyrosine kinase inhibitors. Attention must be paid to concomitant administration of other potentially nephrotoxic agents, to avoid additive nephrotoxicity in these patients.

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### Table 1. The effect of imatinib on renal histology in both groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control N(%) Mean ±SD N=8</th>
<th>Imatinib N(%) Mean ±SD N=8</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruption of normal architecture</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Glomerular Lesions</td>
<td>Increased Bowman’s space</td>
<td>1(12.5%)</td>
<td>5(62.5%)</td>
</tr>
<tr>
<td>Glomerular segmentation/lobulation</td>
<td>1(12.5%)</td>
<td>4(50.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Loss of epithelium of Bowman’s capsule</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Glomerular hyalinization</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Hypertrophy of glomerular cells</td>
<td>0(0.0%)</td>
<td>1(12.5%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Glomerular Edema</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Glomerular congestion/disruption of capillaries</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Glomerular shrinkage</td>
<td>0(0.0%)</td>
<td>2(25.0%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>0(0.0%)</td>
<td>1(12.5%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Tubular Lesions</td>
<td>Tubular dilation</td>
<td>0(0.0%)</td>
<td>3(37.0%)</td>
</tr>
</tbody>
</table>
### Table 2. Effect of imatinib on the reaction of the renal sections of different groups to PAS.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lesion</th>
<th>Parameter</th>
<th>Control N=8</th>
<th>Imatinib N=8</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Glomerular cells</td>
<td>+</td>
<td>+/-</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Glomerular basement membrane</td>
<td>+</td>
<td>+/++</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tubular cells</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tubular basement membrane</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial tissue</td>
<td>+</td>
<td>+/-</td>
<td></td>
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</table>

* ++, moderate; +, mild; -, negative.
Figure 1a. A photomicrograph of a renal section of control rat (with intake of distilled water alone). Normal architecture of renal glomeruli with intact Bowman’s capsule. Brush bordered cuboidal epithelium lining the proximal convoluted tubules. Simple cuboidal epithelium lining the distal convoluted tubules. (H.&E.×400).

Figure 1b. A photomicrograph of a renal section obtained from control rat with normal medullary renal tubules (H.&E.×250).

Figure 2. A photomicrograph of a renal section of rat from imatinib group shows glomeruli with congested capillaries, decreased Bowman’s space, cloudy degeneration of proximal convoluted tubules, and dilated distal renal tubules. (H.&E.×160).

Figure 3. A photomicrograph of a renal section of rat administered with 75mg/kg of imatinib daily for 30 days. Accumulation of chronic inflammatory cells (lymphocytes and macrophages) in the medulla, and extravasations of RBC. (H.&E.×250).

Figure 4. A photomicrograph of a renal section of rat received 75mg/kg/day/30 days of imatinib with feature of early fibrosis (periglomerular and peritubular), and glomerular atrophy. (H.&E.×250).

Figure 5. A photomicrograph of a renal section of rat received 75mg/kg/day/30 days of imatinib with dilated and congested blood vessel and glomerular shrinkage with appearance of structureless eosinophilic area of necrosis. (H.&E.×250).
Figure 6. A photomicrograph of a renal section of rat administered with imatinib. Dilated juxtamedullary blood vessels, thickening and hyalinization of the blood vessel wall and cloudy degeneration (H.&E.×250).

Figure 7. A photomicrograph of a renal section of rat from imatinib group. Dilated tubules with accumulation of structureless eosinophilic homogenous material in tubular lumen, and dilated blood vessel (H.&E.×250).

Figure 8. A photomicrograph of a renal section of rat treated with imatinib. Dilated tubules with flattened epithelium, presence of sloughed cells in their lumina, and extravasated RBC (Toluidine blue×250).

Figure 9. A photomicrograph of a renal section of rat treated with imatinib with thickening of the blood vessel wall (Toluidine blue×400).

Figure 10. A photomicrograph of a renal section of rat treated with imatinib with evidence of interstitial oedema (homogenous area) and early inflammation (H.&E.×250).

Figure 11a. A photomicrograph of sections from control rats. The normal amount of carbohydrates in cortex (PAS+H×400).
Figure 11b. A photomicrograph of sections from control rats. The normal amount of carbohydrates in medulla (PAS+H×250). Figure 12. A photomicrograph of section from imatinib group. Decrease of total carbohydrates (PAS+H×250).Figure 13a. A photomicrograph of cortical area of control group. (Masson’s Trichrome×250) Figure 13b. A photomicrograph of medullary area of control group. (Masson’s Trichrome×250) Figure 14. A photomicrograph of renal section of imatinib group with cloudy appearance, focal infiltration with inflammatory cells. (Masson’s Trichrome ×400).

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تأثير المعاملة بعقار اليميتانب على نسيج الكلى لدى الجرذان البيضاء

لمى إبراهيم خليل العلاف، حافظ على محمود العشو

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