Cancer is expected to become an increasing problem in patients with end-stage renal failure (ESRF) due to the improved long-term survival and the higher incidence of cancer in such patients. Controlled trials of anticancer therapy in patients with ESRF are often lacking. Therefore, treatment is usually based on an extrapolation of pharmacokinetic data from healthy subjects and case reports on patients with ESRF.

Irinotecan (CPT-11), a member of the camptothecin family, is an inhibitor of topoisomerase I, a nuclear enzyme involved in the unwinding of DNA during cell replication. Therapy with irinotecan has been shown to prolong survival in patients with metastatic colorectal cancer. Several irinotecan dosing schemes are in use. One approach is to administer 300–350 mg/m² every 3 weeks. Another approach is to administer 125 mg/m² weekly for 4 weeks followed by no treatment for 2 weeks (4/6), or weekly for 3 weeks followed by 1 week with no treatment (3/4).

The pharmacokinetics of irinotecan are fairly complex. After intravenous administration, irinotecan is converted to several metabolites, including the active metabolite SN-38 (by the carboxylesterase 2 in tissue) and the inactive metabolite APC (by CYP3A4). Eventually, SN-38 is converted to the inactive SN-38 glucuronide (SN-38G) by UDP-glucuronosyltransferase (Figure 1). For patients with renal insufficiency, irinotecan does not seem to need dose modification, since it and its metabolites are excreted mainly into bile, whereas only relatively small amounts are recovered in the urine (irinotecan 21%, SN-38 0.4%, SN-38G 3.4%). However, despite these expectations, severe toxicity has been reported in patients with ESRF, even with reduced doses. Furthermore, recent data suggest a relationship between renal function and irinotecan-induced neutropenia.

Our report details the case of a patient with metastatic colorectal cancer and ESRF who was successfully treated with irinotecan.

**Case Report**

A 64-year-old man (78 kg, body surface area 1.80 m²) with ESRF due to diabetic nephropathy was undergoing long-term hemodialysis 3 times a week. He presented with...
a hepatic lesion (diameter 6 cm) that was consistent with a metastatic lesion. Seven years earlier, he had undergone an anterior resection of the rectum and received adjuvant chemotherapy due to rectal adenocarcinoma. Current cytological analysis of the hepatic lesion showed malignant epithelial neoplasia consistent with colorectal carcinoma. Concomitant diseases included diabetes mellitus, arterial hypertension, peripheral arterial disease, and a history of heparin-induced thrombocytopenia type II. His medication comprised furosemide, enalapril, calcitriol, calcium acetate, and insulin. Laboratory values are reported in Table 1.

The clinicians decided to administer palliative chemotherapy with reduced-dose intravenous irinotecan (50 mg/m² weekly for 3 weeks, repeated after a pause of 1 week). Comedication comprised intravenous ondansetron 8 mg and dexamethasone 8 mg, and subcutaneous atropine 0.25 mg. Due to the patient’s good tolerance (only grade I diarrhea according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events, v3.0), the dose was increased to 80 mg/m² after 2 cycles. During therapy at this dose, the patient experienced grade I leukopenia, grade II diarrhea that responded immediately to loperamide, and grade II anemia that led to the erythropoietin dosage being increased. Diagnostic tests of the hepatic lesion using computed tomography and ultrasound after 2 and 6 treatment cycles showed stable disease. The carcinoembryonic antigen (CEA) value decreased to 40% of its pretreatment level (Figure 2). Eventually, chemotherapy was stopped and the patient was monitored clinically. Ultrasound of the hepatic lesion indicated stable disease at 8 months and progressive disease accompanied by an increase in CEA at 11, 14, and 16 months after the beginning of chemotherapy. The patient decided against further chemotherapy and died 16.5 months after the start of D, Czock et al.

Methods

After informed consent had been obtained from the patient, blood was drawn during and after administration of the first irinotecan dose at predefined times over a period of 48 hours. An additional 4-hour hemodialysis session was performed on the day after irinotecan administration, using a standard polysulfone dialysis membrane (1.3 m², F6HPS, Fresenius Medical Care, Bad Homburg, Germany), with a blood flow rate of 210 mL/min, dialysate flow rate of 500 mL/min, and an ultrafiltrate flow rate of 695 mL/h. Lentinulin 2 mg was used for anticoagulation. During hemodialysis, predialyzer, postdialyzer, and dialysate concentrations of irinotecan and SN-38 were measured. The blood was centrifuged immediately and the plasma fraction was collected and frozen at –20 °C until analysis. Urine was collected over 24 hours. Significant recirculation within the patient’s hemodialysis shunt was excluded by measuring and analyzing urea in predialyzer, postdialyzer, and peripheral plasma.

Plasma concentrations of irinotecan and SN-38 were measured by a high-performance liquid chromatography method with fluorescence detection, as described by Poujol et al. The SN-38G concentrations were determined as the change in SN-38 concentrations following incubation (2 h at 37 °C) with β-glucuronidase. The linearity of the procedure was established up to 200 µg/L for SN-38 and up to 2000 µg/L for irinotecan. The lower limit of quantitation for both substances was 0.5 µg/L. The intra- and interassay imprecision percentages were, respectively, less than 4% and less than 7% for irinotecan, and less than 6% and less than 9% for SN-38. Inaccuracy was less than 6% and less than 5%, respectively.

Pharmacokinetic parameters were calculated using non-compartmental methods. The area under the curve (AUC) was calculated using the linear-trapezoidal rule (up to the start of hemodialysis) and extrapolated to infinity using the slope of the terminal concentration decline. Total body clearance without hemodialysis was calculated as CL_{adj} = D/AUC. In the case of a metabolite, the calculated clearance should be interpreted as an apparent clearance CL(m)/fm, where fm is the fraction of the administered drug that is converted to the metabolite. The half-lives during (t_{1/2on}) and between (t_{1/2off}) hemodialysis sessions were estimated by linear regression of the logarithmically transformed data. In addition, commonly applied ratios of SN-38, irinotecan, and SN-38G were calculated.

Extracorporeal clearance (CL_{extra}) was calculated using the standard equation (Eq. 1), where C_{plasma,in} and C_{plasma,out} are the pre- and postdialyzer plasma concentrations and Q_{plasma,in} and Q_{plasma,out} are the plasma flow rates in and out of the dialyzer. The plasma flow after 2 cycles. During therapy at this dose, the patient experienced grade I leukopenia, grade II diarrhea that responded immediately to loperamide, and grade II anemia that led to the erythropoietin dosage being increased. Diagnostic tests of the hepatic lesion using computed tomography and ultrasound after 2 and 6 treatment cycles showed stable disease. The carcinoembryonic antigen (CEA) value decreased to 40% of its pretreatment level (Figure 2). Eventually, chemotherapy was stopped and the patient was monitored clinically. Ultrasound of the hepatic lesion indicated stable disease at 8 months and progressive disease accompanied by an increase in CEA at 11, 14, and 16 months after the beginning of chemotherapy. The patient decided against further chemotherapy and died 16.5 months after the start of chemotherapy, presumably due to progressive disease.

![Figure 1. Schematic of irinotecan metabolism.](image-url)

Figure 1. Schematic of irinotecan metabolism. Irinotecan is converted to the active metabolite SN-38 and to the inactive metabolite APC. SN-38 is converted to the inactive metabolite SN-38G. MDR = multidrug-resistant protein; MRP = multidrug-resistant related protein; OATP = organic anion transporting polypeptide; UGT = UDP-glucuronosyltransferase.)
rates were calculated based on the blood flow rate ($Q_{\text{blood}}$), the hematocrit (Hct), and the ultrafiltration rate ($Q_{\text{UF}}$) as $Q_{\text{plasma,in}} = [1 – \text{Hct}] \cdot Q_{\text{blood}}$ and $Q_{\text{plasma,out}} = Q_{\text{plasma,in}} – Q_{\text{UF}}$.

$$\text{CL}_{\text{extra,plasma-based}} = \frac{Q_{\text{plasma,out}} \cdot C_{\text{plasma,out}}}{C_{\text{plasma,in}} \cdot Q_{\text{plasma,in}}} \quad \text{Eq. 1}$$

In addition, extracorporeal clearance was calculated based on measured concentrations in the dialysate ($C_{\text{dialysate}}$) and dialysate flow rate ($Q_{\text{dialysate}}$, Eq. 2).

$$\text{CL}_{\text{extra,dialysate-based}} = \frac{Q_{\text{dialysate}} \cdot C_{\text{dialysate}}}{C_{\text{plasma,in}} \cdot Q_{\text{dialysate}}} \quad \text{Eq. 2}$$

The extracorporeally eliminated amount ($A_{\text{extra}}$) was estimated based on $\text{CL}_{\text{extra}}$ (using the higher value of the plasma and dialysate-based estimates) and the area under the concentration curve during hemodialysis ($AUC_{\text{on,T1-T2}}$) as $A_{\text{extra}} = \text{CL}_{\text{extra}} \cdot AUC_{\text{on,T1-T2}}$.

The amount of drug excreted in urine ($A_{\text{e}}$) was calculated based on urine concentrations ($C_{\text{urine}}$) and the volume of urine ($V_{\text{urine}}$). Renal clearance ($\text{CL}_{\text{ren}}$) was calculated by dividing the accumulated amount of drug excreted in the urine ($A_{\text{e}_{0-24}}$) by the AUC during the collection period ($AUC_{0-24}$) as $\text{CL}_{\text{ren}} = \frac{A_{\text{e}_{0-24}}}{AUC_{0-24}}$.

Pharmacokinetic analysis was performed using WinNonlin professional 4.0.1 software (Pharsight Corp., Mountain View, CA) and Excel 2000 (Microsoft Corp., Redmond, WA).

Case reports were identified by PubMed search (1966–June 2008) and by reviewing the references in the those articles. The grades of toxicity were recorded as reported by the original investigators. Agreement with NCI common terminology criteria for adverse events was checked when sufficient clinical information was provided.

**Results**

The measured concentrations of irinotecan, SN-38, and SN-38G after the first dose of irinotecan in our patient are shown in Figure 3. The pharmacokinetic parameters are summarized in Table 2.5-17 Our main findings were a low apparent clearance and a high maximum concentration of SN-38, as well as a high ratio of SN-38 and irinotecan AUCs (Table 2). Although the extracorporeal clearance of irinotecan was 33% of the systemic clearance without hemodialysis, the eliminated amount was only 1.2% of the dose. Similarly, extracorporeal elimination of SN-38 and SN-38G was negligible. Paradoxically, the half-life of SN-38 during hemodialysis appeared to be prolonged. The half-life of SN-38G during hemodialysis was only 50%, but after the end of hemodialysis, a rebound was observed, again indicating negligible extracorporeal elimination.

The patient produced 1.3 L of urine within the first 24 hours. Calculated renal clearance values were 0.092 L/h/m$^2$, 0.056 L/h/m$^2$, and 0.063 L/h/m$^2$ for CPT-11, SN-38, and SN-38G, 2–3%, respectively, of normal renal clearance values.18

**Discussion**

Our main finding is a surprisingly low apparent clearance of SN-38, leading to a relatively high exposure to this metabolite. The dose-adjusted AUC for SN-38 in our patient was 4.3 h•µg/L per mg of irinotecan. In subjects with normal renal function, a value of about 1 h•µg/L per mg of irinotecan was observed.19 Similarly, the maximum SN-38 concentration of 0.4 µg/L per mg of irinotecan in our patient was much higher compared with the average of 0.1 µg/L per mg of irinotecan.15,16 A maximum SN-38 concentration over 0.21 µg/L...
per mg of irinotecan was observed in only 3% of patients. These findings are in contrast to the results of Venook et al., who reported unchanged pharmacokinetics in patients with renal impairment. However, patients in that study had an average creatinine clearance of 41 mL/min and patients with creatinine clearance below 21 mL/min were not included.

In contrast to the markedly reduced SN-38 clearance in our patient, the observed half-life was within the normal range. This can be explained by the pharmacokinetics of SN-38. Despite apparently linear pharmacokinetics, exposure to SN-38 appears to be formation-rate limited. Consequently, the observed decline in SN-38 concentration reflects metabolite formation rather than elimination. Thus, impaired elimination conditions might not affect the observed decline in concentration to a significant degree. Therefore, analyzing half-lives alone may be unreliable in detecting altered metabolite disposition in hemodialysis subjects. Instead, one should consider half-life and clearance in any analysis of such data.

The mechanisms leading to reduced apparent clearance (CL(m)/fm) include reduced elimination capacity and increased systemic availability. We hypothesize that both mechanisms might play a role for SN-38 in patients with ESRF. SN-38 is eliminated by conversion to SN-38G by UDP-glucuronosyltransferase within the hepatocyte (Figure 1). SN-38 is transported into the hepatocyte by the organic anion transporting polypeptide OATP1B1 (OATP2, OATP-C). The functional significance of this uptake process, which is a prerequisite for subsequent intracellular metabolism, is indicated by the effects of OATP1B1 polymorphisms on SN-38 pharmacokinetics. Uremic toxins have been shown to inhibit OATP1B1 in vitro. It might therefore be expected that uremic toxins in patients with ESRF could similarly affect SN-38 elimination by inhibiting uptake into hepatocytes. In addition, systemic availability of SN-38 might be increased in patients with ESRF. Normally, a fraction of irinotecan is converted to the inactive metabolite APC by CYP3A4 within hepatocytes. If this uptake were inhibited, more irinotecan would be available for conversion to SN-38 by tissue carboxylesterase 2. In contrast, it appears unlikely that the expectedly low renal clearance in our patient explains the low apparent clearance of SN-38 to a relevant extent, considering the small amount of SN-38 recovered in the urine of patients with normal renal function. The relative contribution of the renal clearance to the total clearance of SN-38 cannot be calculated, unfortunately, since the fraction of the administered drug that is converted to the metabolite (fm) is not known.

The extracorporeal removal of irinotecan, SN-38, and SN-38G (<1% of the dose) was not clinically significant in our patient, which can be explained by the high level of plasma binding of both irinotecan and SN-38. Paradoxically, the half-life of SN-38 during hemodialysis even appeared to be prolonged. The reason for this observation remains unclear, but might be explained by hemoconcentration, since 1.9 L of ultrafiltrate was removed during hemodialysis.

Two methods were used to calculate hemodialysis clearance. For SN-38 and SN-38G, the dialysate-based estimate was lower compared with the plasma-based estimate. This can be explained by adsorption to the dialyzer membrane. Interestingly, for irinotecan, the dialysate-based estimate was higher compared with the plasma-based estimate. This can be the case for drugs that are bound to erythrocytes and are released from erythrocytes quite rapidly when the drug is removed from the plasma. In fact, irinotecan binding to erythrocytes has been described.

Importantly, the total amount of drug removed by hemodialysis depends on drug concentrations, thus on the timing of hemodialysis. In our patient, approximately 1% of irinotecan was removed by hemodialysis. Extrapolation based on data from our patient showed that hemodialysis could remove up to 10% of irinotecan if the infusion were to be started at the beginning of the hemodialysis session (data not shown). This amount would still most probably not be clinically significant, but we suggest that irinotecan be administered on the day before the next hemodialysis session.

A review of published case reports of irinotecan in patients with ESRF indicates that weekly doses of 50–80 mg/m² were generally tolerated, whereas even single doses of more than 125 mg/m² were associated with serious adverse events (Table 3).

Taken together, our results indicate an increased exposure to SN-38 in patients with ESRF, which might explain the increased risk of adverse events as described in case reports. However, since our patient was not genotyped, the presence of a polymorphism leading to the observed pharmacokinetics independently from renal function cannot be excluded. Furthermore, even in patients with normal renal function, both grade III or IV diarrhea and grade III or IV neutropenia were observed in 31% of cases. In addition, a
publication bias regarding previous case reports cannot be excluded.

We conclude that reduced-dose irinotecan administered weekly for 3 weeks followed by a pause of 1 week is feasible in the palliative therapy of metastatic colorectal cancer in patients with ESRF. Based on our case and other published cases, an initial dose of 80 mg/m² (which is approximately two-thirds of the standard dose) might be considered. Controlled trials of anticancer therapy in patients with ESRF are desirable, since pharmacokinetic extrapolations based on the renal excretion in healthy subjects may be unreliable.

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References


Table 2. Pharmacokinetic Parameters of Irinotecan and Its Metabolites

<table>
<thead>
<tr>
<th>Drug/ Metabolite</th>
<th>Parameter</th>
<th>Value</th>
<th>Literature Values (normal renal function)</th>
</tr>
</thead>
</table>
| Irinotecan (CPT-11) | CL<sub>off</sub> (L/h) | 21.5 | 12.4–17.5<sup>a</sup>,12-14 <br> CL<sub>off</sub> (L/h/m²) | 12.0 | 6.4–17.5<sup>a</sup>,12-14 <br> t<sub>1/2-off</sub> (h) | 7.3 | 7.1–14<sup>a</sup>,12-14 <br> t<sub>1/2-on</sub> (h) | 7.5 | 7.1–14<sup>a</sup>,12-14 <br> CL<sub>extra,plasma-based</sub> (L/h)<sup>b</sup> | 3.4 | 3.4–7.6<sup>a</sup>,15-16 <br> CL<sub>extra,dialysate-based</sub> (L/h)<sup>b</sup> | 7.2 | 3.4–7.6<sup>a</sup>,15-16 <br> A<sub>extra</sub> (mg) | 1.0 | 1.0–2.0<sup>a</sup>,16 <br> SN-38 | CL(m)/f<sub>m-off</sub> (L/h) | 233.7 | 380.8–497<sup>a</sup>,13,17 <br> CL(m)/f<sub>m-off</sub> (L/h/m²) | 130.1 | 13.4–30.2<sup>a</sup>,15-16 <br> t<sub>1/2-off</sub> (h) | 20.3 | 0.4–11.4<sup>a</sup>,16 <br> C<sub>max</sub> (µg/L per mg) | 0.4 | 0.4–11.4<sup>a</sup>,16 <br> SN-38/CPT-11 (%)<sup>d</sup> | 9.2 | 2.8 ± 1.2<sup>12</sup> <br> SN-38/SN-38G (%)<sup>d</sup> | 13.0 | 7.9 ± 5.7<sup>12</sup> <br> t<sub>1/2-on</sub> (h) | 60.0 | 60.0 <br> CL<sub>extra,plasma-based</sub> (L/h)<sup>b</sup> | 1.9 | 1.9–5.8<sup>a</sup>,16 <br> CL<sub>extra,dialysate-based</sub> (L/h)<sup>b</sup> | 1.5 | 1.9–5.8<sup>a</sup>,16 <br> A<sub>extra</sub> (mg) | 0.04 | 0.04 <br> SN-38G | CL(m)/f<sub>m-off</sub> (L/h) | 30.3 | 35.7<sup>13</sup> <br> CL(m)/f<sub>m-off</sub> (L/h/m²) | 16.9 | 16.9 <br> t<sub>1/2-off</sub> (h) | 11.7 | 12.7–23.5<sup>a</sup>,14,15 <br> t<sub>1/2-on</sub> (h) | 5.9 | 5.9 <br> CL<sub>extra,plasma-based</sub> (L/h)<sup>b</sup> | 3.3 | 3.3–6.9<sup>a</sup>,15-16 <br> CL<sub>extra,dialysate-based</sub> (L/h)<sup>b</sup> | 1.9 | 3.3–6.9<sup>a</sup>,15-16 <br> A<sub>extra</sub> (mg) | 0.5 | 0.5 <br>

A<sub>extra</sub> = extracorporeally eliminated amount; CL<sub>extra,dialysate-based</sub> = extracorporeal clearance (estimated based on dialysate concentrations); CL<sub>extra,plasma-based</sub> = extracorporeal clearance (estimated based on plasma concentrations); CL(m)/f<sub>m-off</sub> = apparent total body clearance of a metabolite without hemodialysis; CL<sub>off</sub> = total body clearance without hemodialysis; C<sub>max</sub> = maximum plasma concentration; t<sub>1/2-off</sub> = half-life without hemodialysis; t<sub>1/2-on</sub> = half-life during hemodialysis.

<sup>a</sup>Range of mean values.
<sup>b</sup>Mean of 2 measurements.
<sup>c</sup>Calculated assuming a mean body surface area of 1.73 m².
<sup>d</sup>Calculated using the areas under the curve; mean ± SD.


22. Han JY, Lim HS, Shin ES, et al. Influence of the organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharma-

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**Table 3. Summary of Case Reports on Use of Irinotecan in Metastatic Colorectal Carcinoma and End-Stage Renal Failure**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)</th>
<th>Dose (mg/m²)</th>
<th>Concomitant Therapy</th>
<th>Interval</th>
<th>Doses</th>
<th>Toxicity (type, grade)</th>
<th>Response</th>
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<tr>
<td>26</td>
<td>45</td>
<td>50</td>
<td>fluorouracil, leucovorin</td>
<td>weekly</td>
<td>1 dose</td>
<td>neutropenia IV</td>
<td>partial remission, ↓CEA</td>
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<tr>
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<td>55</td>
<td>50</td>
<td>fluorouracil, leucovorin</td>
<td>2 weekly</td>
<td>4 doses</td>
<td>neutropenia IV</td>
<td>progressive disease</td>
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<td>80</td>
<td>weekly</td>
<td>mild</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>weekly</td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>weekly</td>
<td>diarrhea IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>74</td>
<td>50</td>
<td>fluorouracil, leucovorin</td>
<td>weekly (3/5)</td>
<td>3 cycles</td>
<td>neutropenia III</td>
<td>no change, ↓CEA</td>
</tr>
<tr>
<td>Present</td>
<td>64</td>
<td>50</td>
<td>weekly (3/4)</td>
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<td>2 cycles</td>
<td>diarrhea I</td>
<td>stable disease, ↓CEA</td>
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<tr>
<td>case</td>
<td>80</td>
<td>weekly (3/4)</td>
<td></td>
<td></td>
<td>4 cycles</td>
<td>leukemia I, anemia II</td>
<td></td>
</tr>
</tbody>
</table>

CEA = carcinoembryonic antigen.


Irinotecán para Pacientes con Enfermedad Terminal del Riñón

D Czock, F Maximilian Rasche, B Boesler, M Shipkova, y F Keller


EXTRACTO

OBJETIVO: Observar e informar la farmacocinética de irinotecán en un paciente con enfermedad renal terminal y hemodílisis.

RESUMEN DEL CASO: Un paciente de 64 años con cáncer colorectal metastásico recibe tratamiento con irinotecán a razón de 50 mg/m² por semana durante 3 semanas, seguido de un descanso de 7 días. La dosis se incrementa a 80 mg/m² después de dos ciclos. La enfermedad se ha mantenido estable durante el tratamiento. La concentración de CEA disminuyó en un 40% en comparación con los niveles previos. Los parámetros farmacocinéticos calculados indican una clairance aparente disminuida (CL(m)/fm = 130 L/h/m²) y una concentración máxima del metabolito activo SN-38 más baja (Cmax = 0.4 µg/L por mg) en comparación con valores previamente publicados. La eliminación de irinotecán y sus metabolitos por la hemodiálisis fue insignificante.

DISCUSIÓN: La razón para la baja eliminación del metabolito activo de irinotecán aún no está clara. Los autores sugieren que las toxinas urémicas podrían estar inhibiendo el transportador OATP1B1. Este mecanismo podría explicar la toxicidad excesiva por irinotecán tal como ha sido informado en reportes previos de pacientes en hemodiálisis.

CONCLUSIONES: Los autores concluyen que la dosis de irinotecán para pacientes con enfermedad renal terminal debe ser aproximadamente 2 terceras partes de la dosis estándar semanal.

Traducido por Astrid J García-Ortiz