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# Benefit-Risk Assessment of Irinotecan in Advanced Colorectal Cancer

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## Abstract

Irinotecan exerts its cytotoxic activity through inhibition of the nuclear enzyme topoisomerase I. It has been approved in most countries worldwide for treatment of patients with advanced colorectal cancer (CRC). Activity is seen in previously untreated patients and in patients refractory to fluorouracil treatment, whether it is given alone or in combination with other cytotoxic drugs. Irinotecan was first developed in patients refractory to fluorouracil. Activity in terms of tumour responses and patient benefit was seen in several phase II trials that used either a weekly or a three-weekly schedule. In two randomised trials (irinotecan vs best supportive care, and irinotecan vs an infused fluorouracil-based regimen), irinotecan prolonged median survival by approximately 2.5 months without any deterioration in quality-of-life. It was later studied in previously untreated patients with advanced CRC in combination with fluorouracil/folinic acid (leucovorin). In three large randomised trials, median time to tumour progression was prolonged by

approximately 2.5 months and overall survival by about 2.5 months compared with fluorouracil/folinic acid alone. Tumour responses were also seen more frequently in the irinotecan arm (35–40% vs 20%). Again, quality-of-life scores were not deteriorated by the addition of irinotecan.

Irinotecan has many acute adverse effects. The most prominent and dose limiting being diarrhoea and neutropenia. With irinotecan monotherapy, diarrhoea was seen in 80% of patients and severe grade 3 to 4 diarrhoea occurred in 30–40% of the patients. The severity of diarrhoea can be diminished by preventive actions. Less risk of diarrhoea is generally seen when irinotecan is combined with fluorouracil. Neutropenia is generally short-lived, but may be severe if diarrhoea is also present. This has been noticed particularly when irinotecan has been given in combination with a bolus fluorouracil/folinic acid regimen. Other toxicities include acute cholinergic-like symptoms, nausea and vomiting, and alopecia. In spite of these adverse effects, irinotecan has been accepted as an important first-line treatment for patients with advanced CRC, in combination with, preferably, an infused fluorouracil-based regimen, and has been approved for use as monotherapy in the second-line indication.

Irinotecan (7-ethyl-10-[4(1-piperidino)-1-piperidino] carbonyloxy camptothecin; CPT-11) is a semisynthetic derivative of the plant alkaloid camptothecin. It exerts its cytotoxic activity through inhibition of the nuclear enzyme topoisomerase I. This enzyme facilitates DNA replication and transcription by causing single-strand, protein-bridged breaks in DNA, which relieve the torsional strain in the double helix ahead of the replication fork.[1]

Irinotecan has been approved in about 80 countries including Europe, the US and Japan. The drug is indicated for patients with advanced colorectal cancer (CRC): (i) as first-line therapy in combination with fluorouracil and folinic acid (leucovorin) in previously untreated patients; and (ii) as a single agent in patients whose established fluorouracil-containing regimen had failed.

Since its first approval in 1995 in France, it has been increasingly used worldwide. Between November 2002 and November 2003, it was estimated that approximately 68 000 patients were treated. During the past 10 years, since it was first approved, a rough estimate is that about 400 000 patients have been treated. The large majority of those patients were treated for advanced CRC, which is the topic of this report.

Chemotherapy is presently the only systemic treatment that can prolong life in advanced CRC. The wellbeing of the patients can be improved by various supportive care activities, but the most effective way is to obtain tumour regression, or at least disease stabilisation, by chemotherapy. Radiation therapy can be used for some patients, but most have disease at sites where the effects of the possible radiation are limited. Surgery is rarely possible, although it may cure a few patients. Most recently, alternative treatments, particularly monoclonal antibodies such as cetuximab and bevacizumab or small molecules targeting certain cell receptors, have added to the activity of the cytotoxic agents, but they will not replace chemotherapy.

## 1. Benefit Evaluation

### 1.1 Advanced Colorectal Cancer

CRC affects about 1 million patients worldwide annually and thereby ranks third in frequency. Approximately 0.6 million patients die from CRC every year, which corresponds to 8% of cancer-related deaths.[2] When CRC is diagnosed, it is surgically incurable in 20–30% of the patients, mainly because of metastatic spread or tumour overgrowth of a vital organ that prohibits surgical removal. During the first 5–7 years after an apparently curative surgery another 20–40% of the patients will experience recurring cancer, either loco-regionally or at distant sites. With very few exceptions, advanced CRC is a fatal disease. In the absence of curative treatments,

the outcome is poor with, on a population level, a median survival of <6 months and a very low probability to survive beyond 1 or 2 years. In some patients with locally advanced disease or limited liver or lung metastases, radical surgery or occasionally radical radiotherapy can be performed, with a probability of long-term cure.[3] Although survival in non-selected patient groups presently is poorly known, several large international centres today report median survivals exceeding 1.5 years (approaching 2 years) in patients with advanced CRC. Long-term survival is still poor. Increased use of chemotherapy, mainly fluorouracil/folinic acid together with irinotecan and oxaliplatin, is responsible for a major part of this prolongation in median survival, although other factors such as stage migration that is seen in selected series and surgery and general healthcare improvements also contribute.[4]

### 1.2 Treatment with Chemotherapy

The purpose of chemotherapy in advanced CRC is to kill tumour cells and thus induce disease stabilisation or remission. As a consequence, time to disease progression and overall survival are prolonged, symptoms are relieved and quality-of-life (QoL) is improved. These effects are well documented in the literature, and statistically significant gains have been observed with some chemotherapy regimens in individual trials or meta-analyses.[5-10]

Even if the lives of many patients with advanced CRC may be prolonged by several months with chemotherapy, the majority of patients will ultimately die from the disease. This knowledge, and the fear of problematic symptoms later in the course of the disease, is a burden to patients, relatives and close friends. Even if the palliative treatments appear to function well, attaining tumour regression and limited toxicity, there is a need for continuous supportive care. This need increases as the disease advances and fewer treatments remain with sufficient probability to have effect.

### 1.3 Balancing Gains and Costs of Palliative Chemotherapy in Colorectal Cancer – General Aspects

Each advance in the treatment of advanced CRC, including that seen with irinotecan, has been accompanied by additional toxicity and higher economic costs. There is no doubt that the overall gains in terms of longer progression-free and overall survival and QoL improvements achieved with palliative chemotherapy are sufficiently large, in relation to the total costs to the individual and society, to merit routine use of palliative chemotherapy. However, what requires further discussion is whether all incremental gains are sufficiently large to merit routine use. Since trial methodology has improved,[11] including recognition of the need to perform large conclusive trials, there is actually a danger that gains that are not clinically relevant are proven with statistical significance.

It is likely that most clinicians and scientists agree that statistical significance does not necessarily indicate clinical relevance. Still, this conclusion is controversial for two reasons: (i) there is no consensus on whether a minimum size of any gain, in relation to toxicity, inconvenience and other costs, has been defined; and (ii) there is no consensus as to what the most relevant parameter for measuring treatment efficacy is. Emphasis has been placed on 'overall survival' as the primary endpoint in phase III clinical trials in advanced CRC. However, the limitations of overall survival have been discussed and time to tumour progression may be more appropriate.[12,13]

The individual patient's judgement of whether a particular gain is sufficient to make therapy acceptable in light of anticipated treatment burden (including hospital visits, blood tests etc., associated toxicity) is of greatest relevance. Research and clinical experience have shown that patients generally want to be treated for very small incremental gains,[14] which are frequently too small for a doctor or healthcare provider to justify. Many patients facing the outcome of progressive cancer, such as those with advanced CRC, seem to accept treatments which offer very short survival prolongations.

The issue of gains and costs becomes even more difficult when one balances gains on survival against the influence of treatment on tumour-related symptoms or other QoL issues. Again, most patients desire treatment even if the probability of symptom-relief is minute.[14] National guidelines or consensus meeting documents have provided discussions about what minimal gains are acceptable for routine

treatment on a population level.[15-17] These general guidelines should be applied when tumour-controlling or non-tumour-controlling supportive care options are discussed with the individual patient and his or her relatives. Although guidelines cannot be strictly applied when discussing an individual patient, they are useful as a support. The conclusions reached in the guidelines cited above, namely that palliative treatment is not indicated routinely unless: (i) it prolongs survival by at least 30%, or a minimum of 3 months; or (ii) has a likelihood of a clear clinical benefit that will be seen more than occasionally or in >20% of patients, are then valuable in practical applications. The results seen in the trials using irinotecan will be discussed in relation to these guidelines.

Most practising clinicians are increasingly aware of the cost constraints on healthcare budgets. Costs have increased for a number of therapies and other interventions. The costs for anti-cancer drugs have increased substantially and treatments for advanced CRC are no exemption. The extra costs of any new therapy, in this case chemotherapy for advanced CRC, must then be balanced against the gains, such as longer (progression-free) survival, improved wellbeing and potential cost-savings by reduced needs for other (supportive) measures. The number of pharmacoeconomic studies in patients with advanced CRC is limited[18-24] and, although they often claim that one treatment is cost-effective in comparison with other treatments (or supportive care), it is difficult to draw firm conclusions.[25,26] Some of the new treatment options for advanced CRC are very close to the economic limits of what can be accepted, at least in a healthcare system that has the ambition to be loyal to all individuals. The finding that fluorouracil-based therapy prolongs survival by 4–5 months compared with best supportive care,[6,27] was associated with a cost in 1992 of approximately SEK77 000 per quality-adjusted life year (QALY) gained.[18] Although difficult to translate to another currency in 2004, this is equivalent to approximately €10 000 QALY, which is within the acceptable range for a cost-effective treatment option.

### 1.4 Irinotecan as a Single Agent in Fluorouracil Refractory Disease

Fluorouracil-based regimens have been the cornerstone of chemotherapy in advanced CRC for about the past four decades.[28] After one fluorouracil-containing regimen had failed, it was observed that some patients could respond to a modified fluorouracil-based regimen. For example, if the first regimen used bolus fluorouracil, subsequent therapy with infused fluorouracil was frequently used based upon the assumption that the anti-tumour activity was different.[29,30] Responses were seen, but the efficacy of this approach was never evaluated thoroughly. It was not until irinotecan appeared, with an apparently different mode of action, that randomised trials were performed, revealing improved survival. In several phase II studies, irinotecan monotherapy showed activity in patients whose fluorouracil/folinic acid treatment had failed, as well as in chemo-naive patients. Objective responses were seen in about 15% of the patients with a median response duration of 6 months.[31-35] Palliative benefits were noted among responders and those with prolonged disease stabilisations, even if severe toxicity was frequently noted.

The results of two randomised studies, in which irinotecan (350 mg/m$^2$ every 3 weeks) was compared with the best supportive care and the best estimated chemotherapy regimen in patients with fluorouracil refractory cancer, showed a significant benefit for irinotecan in terms of improved survival (table I).[36,37] Several QoL issues favoured the irinotecan-treated patients. Survival without performance status deterioration, without weight loss of >5% and pain-free survival were significantly superior in patients given irinotecan. However, no differences in the mean scores of the various components of the The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire were generally seen in patients who responded. Patients completed the questionnaire at regular intervals prior to a new treatment, i.e. generally not at the times of maximal toxicity after a treatment. The difficulties in interpreting QoL scores in chemotherapy trials in advanced CRC have been discussed elsewhere.[38-40]

**Table I.** Results of randomised phase III trials comparing irinotecan alone with either supportive care or infused fluorouracil (FU) in patients with advanced colorectal cancer failing a fluorouracil-based regimen

| Study | No. of patients | Endpoint | Irinotecan | Infused FU | Supportive care |
|---|---|---|---|---|---|
| Rougier et al.[41] | 267 | Median TTP (months) | 4.2* | 2.9 | |
| | | Median survival (months) | 10.8* | 8.5 | |
| | | 1-year survival (%) | 45% | 32% | |
| Cunningham et al.[36] | 279 | Median survival (months) | 9.2** | | 6.5 |
| | | 1-year survival (%) | 36% | | 14% |

**TTP** = time to tumour progression; * $p < 0.05$ vs FU; ** $p < 0.001$ vs supportive care.

In the single-agent phase I-II trials preceding the phase III trials, several irinotecan schedules were used. In Japan and North America, the drug was often administered as a 90-minute infusion that was received once weekly for 4 consecutive weeks, followed by a 1-week rest,[34] whereas in Europe it was given every third week. The two schedules, using the generally recommended dosages (125 mg/m$^2$ weekly or 350 mg/m$^2$ [300 mg/m$^2$ for patients >70 years of age or who had a WHO performance status of 2] every third week) were compared in a randomised phase III trial that included 291 patients. The two schedules yielded similar efficacy and QoL in patients with fluorouracil refractory CRC.[42] Similar efficacy was also seen in another randomised trial that compared irinotecan fractionated into two doses (days 1 and 10) every 21 days to the regular 21-day schedule.[43] See section 2.2 concerning differences in toxicity profiles.

### 1.5 Irinotecan in Combination with Fluorouracil in First-Line Treatment

Irinotecan has been approved for use together with fluorouracil/folinic acid in first-line metastatic CRC in many countries. Randomised studies have evaluated the addition of irinotecan to bolus and/or infused fluorouracil/folinic acid (48 hr bi-monthly and 24 hr weekly) in first-line treatment of advanced CRC.[44-47] In all studies, the fluorouracil/folinic acid plus irinotecan combination achieved a higher response rate than fluorouracil/folinic acid alone (about 35–40% vs 20%; $p \leq 0.005$), longer times to treatment failure and overall survival (median approximately 2.5 months) [table II]. In one of the trials, an irinotecan alone arm was also included and yielded similar results to the fluorouracil/folinic acid combination.[46]

In another randomised trial (n = 234), irinotecan or methotrexate was added to a fortnightly bolus fluorouracil/folinic acid regimen.[48] More responses (36% vs 20%, $p < 0.001$), longer time to disease progression (7.2 months vs 4.8 months, $p = 0.048$), but no improvement in survival (median 14.8 months for both groups) were seen in the irinotecan arm versus the methotrexate arm.

### 1.6 Subsequent Trials Evaluating Irinotecan, Oxaliplatin and Fluorouracil/Folinic Acid (Leucovorin)

Parallel with the development of irinotecan in advanced CRC, oxaliplatin, a third generation platinum compound, was also investigated in this indication. A combination of oxaliplatin and bolus and infused fluorouracil/folinic acid (FOLFOX-4 regimen) yielded superior results in terms of response rates and time to progression compared with fluorouracil/folinic acid alone as first-line treatment.[49,50] Activity was seen when oxaliplatin was given with fluorouracil/folinic acid in the second-line indication in phase II trials. Several trials have since compared the three presently available active drugs, fluorouracil (generally with folinic acid), oxaliplatin (with fluorouracil/folinic acid) and irinotecan, in different combinations and sequences.

The largest of these trials compared irinotecan with bolus fluorouracil/folinic acid (IFL), FOLFOX-4 and a combination of irinotecan and oxaliplatin (IROX).[51] A higher response rate, longer time to disease progression and longer survival were seen using the FOLFOX-4 regimen (table III). More toxicity, including more toxic deaths, was seen with the bolus IFL regimen (see section 2.3 for details). The IROX regimen produced similar results to the IFL regimen. The clearly longer survival in the FOLFOX-4 arm (19.5 months vs 15.0 months)

**Table II.** Results of randomised phase III trials comparing fluorouracil/folinic acid (leucovorin) with or without irinotecan as first-line treatment of advanced colorectal cancer

| Study | No. of patients | Endpoint | Fluorouracil/ folinic acid | Fluorouracil/folinic acid + irinotecan | Irinotecan |
|---|---|---|---|---|---|
| Douillard et al.[45] | 387 | Median TTP (months) | 4.4 | 6.7*** | |
| | | CR + PR (%) | 22 | 35** | |
| | | Median survival (months) | 14.1 | 17.4* | |
| Saltz et al.[46] | 683 | Median TTP (months) | 4.3 | 7.0** | 4.2 |
| | | CR + PR (%) | 21 | 39*** | 18 |
| | | Median survival (months) | 12.6 | 14.8* | 12.0 |
| Köhne et al.[47] | 430 | Median TTP (months) | 6.3 | 8.8**** | |
| | | Median survival (months) | 16.8 | 20.1[a] | |

a p-Value not reported.

**CR** = complete response; **PR** = partial response; **TTP** = time to tumour progression; * $p < 0.05$; ** $p \leq 0.005$; *** $p < 0.001$; **** $p = 0.0001$.

can be interpreted in different ways, although a likely explanation is the availability of second-line irinotecan after the FOLFOX-4 regimen failed, whereas no proven second-line regimen was available after the IFL regimen failed. In a randomised phase III study in patients whose fluorouracil-based regimen failed, the activity of these three schedules (irinotecan with fluorouracil/folinic acid), oxaliplatin with fluorouracil/folinic acid or irinotecan with oxaliplatin) appeared to be similar.[41]

Another, randomised trial compared irinotecan and oxaliplatin combined with fluorouracil/folinic acid regimens (FOLFIRI and FOLFOX-6, respectively) and second-line therapy was scheduled in both groups.[52] Thus, after progression, a FOLFOX-6 regimen was planned after a FOLFIRI regimen and the FOLFIRI regimen was planned after the FOLFOX-6 regimen. Time to progression after second-line treatment was the primary endpoint. The results showed that there was no difference in the overall response rate to first-line treatment, time to progression after second-line treatment or overall survival between the two sequences (table III). Similarily, preliminary results of an Italian study comparing FOLFIRI and FOLFOX did not detect any difference in efficacy between the regimens.[53]

The bolus IFL regimen, the bolus/infused FOLFIRI regimen and an alternating irinotecan/bolus fluorouracil/folinic acid (Mayo Clinic) regimen were compared in a randomised phase II trial including 154 patients.[54] The anti-tumour activity was similar, but toxicity favoured the FOLFIRI-regimen (for details, see section 2.3).

In phase II trials (some randomised), irinotecan has also been combined with other bolus or infused fluorouracil/folinic acid regimens or oral fluoropyrimidines.[55-62] Response rates and times to progression that are similar to the ones presented previously have been seen.

Recently, it was shown in a large randomised trial that the FOLFOX-4 regimen has activity after failure of the IFL regimen.[63] The activity of FOLFOX-4 was superior to either the fluorouracil/folinic acid deGramont schedule (LV5FU2) or oxaliplatin alone.

## 2. Tolerability Evaluation

### 2.1 Metabolism of Irinotecan

Irinotecan is enzymatically converted by carboxylesterase to its most active cytotoxic metabolite, SN-38.[64] The primary route of metabolism of irinotecan is otherwise through cytochrome P450 (CYP) 3A4, which generates inactive metabolites. However, the biliary excretion of SN-38 after hepatic glucoronidation by UDP-glucuronosyl transferase 1A1 to SN-38G[65] is more important than the metabolic clearance by CYP3A isoforms. The biliary clearance of both SN-38 and SN-38G is mediated by canalicular multispecific anion transporter (cMOAT) and multidrug resistance (MDR1) 8P-glycoprotein.[66,67] The highest levels of carboxylesterase activity in normal human tissues are found in the liver, followed by the gastrointestinal tract.[68] Tumour tissues tend to have lower levels than matched normal tissues. Even if the conversion of

irinotecan within the liver and the gastrointestinal tract is responsible for the majority of SN-38 formation and thus cytotoxic activity, conversion within the tumours may also be relevant, since tumours have limited ability to detoxify SN-38 through glucoronidation.[69] In the bowel, bacterial β-glucoronidase can convert SN-38G back to SN-38, which can be reabsorbed resulting in an enterohepatic recirculation loop. This leads to high concentrations of SN-38 in the small bowel and can be responsible for the late diarrhoea frequently seen after irinotecan therapy (see section 2.2 and section 2.3).[70,71] Since ciclosporin inhibits both cMOAT and MDR1 and, thus, the biliary excretion of SN-38G,[72,73] a clinical trial, CIVIC (Conventional Irinotecan Versus Irinotecan plus Ciclosporin), is planned in the UK to determine if this regimen can reduce irinotecan-associated toxicity.

Individuals with a congenital deficiency of UGT1A1 (Gilbert's syndrome or Crigler-Najjar syndrome type 1 and type 2) are at increased risk of toxicity from irinotecan. These patients, as well as those with significant liver pathology (e.g. serum bilirubin levels >1.5 × upper levels of normal limit [ULN] and AST or ALT >2.5–5 × ULN) have generally been excluded from clinical trials. In an analysis of four trials, total serum bilirubin level was the most relevant predictor of risk of neutropenia.[74] In yet another retrospective analysis of a clinical trial using weekly irinotecan, a modest elevation of serum bilirubin levels (approximately 1.0–1.5 × ULN) was also associated with increased grade 3–4 neutropenia, but baseline serum bilirubin levels did not reliably predict overall irinotecan-related toxicity (or efficacy).[75] Several recent studies have shown that the homogeneous UGT1A1*28 genotype (7/7 genotype) leads to several-fold lower

**Table III.** Results of randomised phase III trials comparing irinotecan and oxaliplatin combinations with different fluorouracil and folinic acid (leucovorin) regimens[a] as first- and second-line treatment in advanced colorectal cancer

| Study | No. of patients | Indication | Outcome | Bolus IFL | FOLFIRI | FOLFOX-4 | FOLFIRI–FOLFOX-6 | FOLFOX-6–FOLFIRI | IROX |
|---|---|---|---|---|---|---|---|---|---|
| Goldberg et al.[51] | 795 | first-line | Median TTP (months) | 6.9 | | 8.7** | | | 6.5 |
| | | | CR + PR (%) | 31 | | 45* | | | 35 |
| | | | Median survival (months) | 15 | | 19.5 | | | 17.4 |
| Tournigand et al.[52] | 220 | first- and second-line | CR + PR, first-line (%) | | | | 56 | 54 | |
| | | | CR + PR (%), second-line | | | | 15 | 4[b] | |
| | | | TTP after second-line (months) | | | | 14.4 | 11.5[b] | |
| | | | Median survival (months) | | | | 20.4 | 21.5[b] | |
| | | | Surgery of metastases | | | | 8 (7%) | 21 (19%)[b] | |
| Rougier et al.[41] | 191 | second-line | Median TTP (months) | | 3.2 | 4.7 | | | 4.2 |
| | | | CR + PR (%) | 11 | 21[b] | | | | 15 |
| | | | Median survival (months) | | 12.2 | 11.5 | | | 11.0 |

a Bolus IFL: irinotecan 125 mg/m², bolus fluorouracil 500 mg/m², folinic acid 20 mg/m² weekly for 4 weeks, 1 week rest; FOLFOX-4: oxaliplatin 85 mg/m² d 1, folinic acid 200 mg/m² d 1 + 2, fluorouracil bolus 400 mg/m² d 1 + 2, fluorouracil continuous infusion 1200 mg/m²/44h, new treatment d 15; IROX: irinotecan 200 mg/m², oxaliplatin 85 mg/m² q3w; FOLFIRI: irinotecan 180 mg/m² d 1, folinic acid 200 mg/m² d 1 + 2, fluorouracil bolus 400 mg/m² d 1+ 2, fluorouracil continuous infusion 1200 mg/m²/44h, new treatment d 15; FOLFOX-6: oxaliplatin 100 mg/m² d 1, folinic acid 200 mg/m² d 1, fluorouracil bolus 400 mg/m² d1, fluorouracil continuous infusion 2400–3000 mg/m²/44h, q2w.

b Difference between treatment groups not statistically significant.

**CR** = complete response; **PR** = partial response; **q*x*w** = every 'x' weeks; **TTP** = time to tumour progression; * $p < 0.05$; ** $p = 0.0001$.

glucoronidation of SN-38 than the wild-type sequence (6/6 genotype) and increased risk of severe neutropenia.[76-78]

### 2.2 Single Agent Irinotecan

The dose-limiting toxicity seen in the phase I trials was delayed-onset diarrhoea. Another important toxicity was neutropenia (dose-limiting in some of the trials), which occasionally became serious and lethal if combined with diarrhoea, nausea/vomiting, asthenia, alopecia and acute cholinergic-like symptoms.[31-37] These toxicities were seen irrespective of the irinotecan schedule, although it was later found that the proportions differed. Overall, any grade of these toxicities was seen in about 80% of patients and grades 3–4 toxicity were seen in 20–40% of patients. Using the weekly schedule for 4 weeks followed by a 2-week rest, the recommended dose for further testing in the phase II and III trials, and later approved in Europe and the US, was 125 mg/m$^2$ (100 mg/m$^2$ in Japan).[79,80] The 3-weekly schedule dose was 350 mg/m$^2$ (300 mg/m$^2$ for patients >70 years of age).[81] Although patients with good performance status could tolerate higher doses of up to 500 mg/m$^2$ following a selective first cycle at a lower dose,[82,83] some later trials have found that the standard dosage of 350 mg/m$^2$ every third week is too toxic.[84] A lower starting dosage, 250 mg/m$^2$ every third week, with dose escalation in the absence of any toxicity is better tolerated and appears to have the same efficacy.[85] Similar efficacy, but lower toxicity, was also demonstrated when irinotecan was given every 10 days rather than every 3 weeks.[43]

### 2.3 Irinotecan with Fluorouracil and Folinic Acid

When irinotecan was combined with fluorouracil/folinic acid, delayed-onset diarrhoea was the dose-limiting toxicity in phase I trials,[86] irrespective of fluorouracil/folinic acid schedule (bolus, infused, oral tegafur uracil/folinic acid). It was observed that the incidence and severity of diarrhoea was less with the irinotecan/fluorouracil/folinic acid combination than when irinotecan was given alone, in spite of the fact that fluorouracil/folinic acid also causes diarrhoea. The sequence of administration, favouring irinotecan first, was also relevant.[56] Neutropenia, nausea, vomiting, asthenia, alopecia and acute cholinergic-like symptoms were also frequently seen although, again, the incidences were lower than when using irinotecan alone; thus, combination therapy was better tolerated than irinotecan monotherapy. The relative incidence of these adverse events also differed according to the fluorouracil schedule. It was observed that the recommended dose for further testing, used in phase I trials, had to be modified when subsequently tested in phase II and III (doses of either irinotecan or fluorouracil lowered by 10–20%).

In the following sections (2.4 to 2.7), the major toxicities, seen in the phase I–II trials, are described first, giving overall frequencies, some particular characteristics, outcome, precautions and actions taken to prevent or relieve them. Thereafter, the incidence of each of the major adverse effects is given as reported in the randomised multicentre phase III trials. The frequencies and the causality of adverse events are best evaluated in these trials against the background of 'adverse events' seen in patients with progressive advanced CRC.

### 2.4 Acute Cholinergic-Like Syndrome

A very typical, sometimes problematic, but not dose-limiting, toxicity has been an early onset of cholinergic-like symptoms. These may occur shortly after drug administration and include various symptoms, such as diaphoresis, chills, malaise, dizziness, visual disturbances, lacrimination, salivation, bradycardia, abdominal cramps and diarrhoea. In order to be classified as belonging to the acute cholinergic-like symptoms, the diarrhoea must have occurred within 24 hours after drug administration. These symptoms are believed to be caused by inhibition of cholinesterase activity, which has been attributed to the piperidine structure of the irinotecan molecule.[87] Severe symptoms may occur in up to 10% of patients, less severe symptoms in >80% of patients, sometimes after the first drug injection.[88] The symptoms are mostly short-lasting and respond within minutes to administration of atropine (0.25–1mg subcutaneously). Experience has shown that, with further administrations, most patients develop these symptoms. Therefore, although not routinely recommended in the prescribing information

for irinotecan, many nurses prophylactically give atropine from the very first treatment. If a patient has had any of the symptoms once, prophylactic treatment during subsequent cycles is highly recommended.

### 2.5 Delayed Diarrhoea

Delayed diarrhoea occurring more than 24 hours after drug administration is one of the most clinically relevant adverse effects and it has been observed in most (>80%) patients treated with irinotecan.[88] Severe (grade 3 or 4 National Cancer Institute Common Toxicity Criteria [NCI-CTC]) diarrhoea has generally occurred in about one-third of patients who have been managed according to recommended guidelines. These guidelines recommend that all patients should start loperamide at the first sign of loose stools. The starting dose should be 4mg, followed by 2mg every 2 hours until 12 hours beyond the last episode of diarrhoea. Loperamide should not be given as prophylaxis to asymptomatic patients, since it may prolong the residence time of irinotecan metabolites in the bowel. Patients with diarrhoea that persists for >48 hours or diarrhoea associated with grade 3 or 4 neutropenia, whether fever is present or not, should receive a broad spectrum oral antibacterial. In addition, hospitalisation may be required, especially in cases of long-lasting severe diarrhoea with neutropenic fever. A combination of diarrhoea and neutropenia may be life-threatening and has resulted in treatment-related deaths.[89] This was particularly pronounced when irinotecan was combined with a bolus fluorouracil/folinic acid regimen.

### 2.6 Neutropenia

Neutropenia occurring after irinotecan administration is reversible, not cumulative and virtually always of short duration. Grade 3 or 4 neutropenia occurs in approximately one-third of patients.[31-37] Since it is of short duration it seldom results in neutropenic fever, although this occasionally happens and it may be severe, particularly if delayed diarrhoea is also present. In order to limit severe neutropenia and neutropenic fever, two large randomised trials evaluated whether prophylactic G-CSF administration or prophylactic use of antibacterials was of benefit. This was not found to be the case, although the incidence and severity of neutropenia were reduced by both treatments.[90,91]

Since neutropenia and delayed diarrhoea are commonly seen and may be severe, analyses of predictive factors have been performed in several trials. Poor performance status, multiple organ involvement, low blood haemoglobin levels, elevated serum bilirubin levels (1.5 × ULN) or increased white blood cells counts at baseline, prior abdomino-pelvic radiotherapy, chronic inflammatory bowel disease and ongoing signs of subileus have all been identified as being of relevance in different trials. In many trials, these factors have been exclusion criteria for trial participation. These factors are also considered of great relevance prior to the decision to offer a patient single dose irinotecan treatment or irinotecan with a fluorouracil-based regimen. However, it has not been possible to date to identify subgroups of patients with very low (<10%) or high (>50%) risk of either neutropenia or delayed diarrhoea. In the near future, pharmacogenetic analysis of UGT1A1 will likely be of value in excluding patients with the greatest risk of severe toxicity.[92] Whether patients with known UGT1A1 7/7 genotype can safely be given lower doses of irinotecan or particular schedules is not known. Chronic inflammatory bowel disease together with known hypersensitivity to irinotecan are contraindications to treatment.[88]

### 2.7 Incidence of Adverse Effects in the Major Randomised Trials

Grade 3 and 4 adverse effects occurring in clinical trials with fluorouracil/folinic acid, irinotecan, oxaliplatin alone or in combination as first- or second-line therapy are summarised in table IV, table V and table VI. In the second-line studies,[36,37] it can be seen that irinotecan resulted in more diarrhoea, neutropenia and nausea/vomiting than was seen with supportive care or infused fluorouracil (table IV). The relative frequencies of these adverse events are slightly lower than those that were seen in the previous phase II trials, which can likely be explained by stricter exclusion criteria that excludes patients with large tumour burdens, e.g. noticed as poor performance status and low blood haemoglobin levels. Of course, acute cholinergic-

**Table IV.** Number (%) of patients experiencing grade 3 or 4 adverse effects with irinotecan monotherapy (350 mg/m$^2$/3 weeks) in the second-line indication in the two pivotal phase III trials

| Adverse event | Cunningham et al.[36] | | Rougier et al.[37] | |
|---|---|---|---|---|
| | supportive care (n = 90) | irinotecan (n = 189) | irinotecan (n = 127) | infused fluorouracil (n = 129) |
| Anaemia | 6 (7) | 13 (7) | 8 (6) | 4 (3) |
| Neutropenia | 0 | 42 (22) | 18 (14) | 3 (2) |
| Febrile neutropenia | 0 | 6 (3) | 7 (6) | 2 (2) |
| Thrombocytopenia | 0 | 2 (1) | 5 (4) | 2 (2) |
| Nausea | 3 (3) | 26 (14) | 14 (11) | 5 (4) |
| Vomiting | 7 (8) | 26 (14) | 18 (14) | 6 (5) |
| Diarrhoea | 5 (6) | 42 (22) | 28 (22) | 14 (11) |
| Constipation | 7 (8) | 19 (10) | 10 (8) | 8 (6) |
| Cholinergic-like syndrome | 0 | 23 (12) | 2 (2) | 0 |
| Asthenia | 17 (19) | 28 (15) | 17 (13) | 15 (12) |
| Mucositis | 1 (1) | 4 (2) | 3 (2) | 7 (5) |
| Anorexia | 6 (7) | 9 (5) | 7 (6) | 5 (4) |
| Cutaneous signs | 0 | 4 (2) | 1 (1) | 11 (8) |
| Neurological symptoms | 12 (13) | 23 (12) | 11 (9) | 5 (4) |
| Cardiovascular symptoms | 3 (3) | 15 (8) | 5 (4) | 2 (2) |
| Pain (excluding abdominal) | 24 (22) | 36 (19) | 21 (17) | 17 (13) |
| Abdominal pain | 14 (16) | 26 (14) | 11 (9) | 10 (8) |
| Alopecia | NA | NR | 14 (11) | 1 (1) |
| Non-neutropenic infection | 3 (3) | 17 (9) | 1 (1) | 5 (4) |
| Drug-related deaths | NA | 2 (1) | 0 | 1 (1) |

**NA** = not applicable; **NR** = not reported.

like symptoms were not seen in the absence of irinotecan treatment. In contrast, asthenia and abdominal pain, noted quite frequently in the phase I/II trials, were not more common than in the control groups. However, this does not mean that irinotecan can not result in asthenia. Asthenia, as well as abdominal pain, is frequently associated with tumour progression, which is seen more frequently in both control groups. Drug-related deaths were infrequent and not more common than with infused fluorouracil.

In the pivotal trials that compared fluorouracil/folinic acid with or without irinotecan,[45,46] diarrhoea was more common with irinotecan than without; however, it was less frequent than in the irinotecan alone arm (table V). In one trial, neutropenia was more common with combination therapy (irinotecan plus infused fluorouracil/folinic acid),[45] whereas in the other,[46] neutropenia was more common with the bolus fluorouracil/folinic acid schedule without irinotecan than with combination therapy. The incidence of grade 3 or 4 neutropenia was 66% with the bolus fluorouracil/folinic acid administration schedule.

These two irinotecan/fluorouracil/folinic acid regimens[45,46] became reference treatments and were used in a series of subsequent trials that reported toxicity. The bolus IFL regimen (irinotecan 125 mg/m$^2$, folinic acid 20 mg/m$^2$, fluorouracil 500 mg/m$^2$ once weekly for 4 weeks every 6 weeks) was predominantly used in the US, whereas the bolus/infused FOLFIRI regimen (irinotecan 180 mg/m$^2$ day 1, folinic acid 200mg/m$^2$ and fluorouracil bolus 400 mg/m$^2$ days 1, 2 and fluorouracil infusion 1200 mg/m$^2$ for 44 hours starting day 1 every 14 days) was used predominantly in Europe.

In two US trials that used IFL, an unexpectedly high number of early deaths was seen. Those deaths were independently reviewed.[89] In the adjuvant trial, IFL had a 3-fold higher rate of treatment-induced or treatment-exacerbated deaths than patients treated on the control Roswell Park fluorouracil/folinic acid arm (2.5% vs 0.8%). The second trial in metastatic disease has been reported in

full[51] and toxicity data are given in table VI. The deaths seen in the trials were either gastrointestinal syndrome-induced or exacerbated, or vascular syndrome-induced or exacerbated. It was found that the precautions were not always followed by all participating centres in the trials.[89] The concept of 60 days mortality was introduced. In metastatic disease, these are a mixture of treatment-related, disease-related and other deaths, whereas such deaths are rarely associated with the underlying cancer in the adjuvant situation. In the IFL-arms, most deaths were treatment-related.

A similar rate of early deaths has not been seen in a the European adjuvant trial using FOLFIRI. The European experience in metastatic disease also shows a very low risk of treatment-related deaths when FOLFIRI is used as opposed to that observed in the US trials with the IFL regimen.[93] In the trial comparing FOLFIRI and FOLFOX-6, a similar rate of 60-day mortality was seen (3–4%, table VI), but only one death (1%), seen in the FOLFOX-6 arm, was treatment-related.[52] Similarly, in a randomised phase II trial, the FOLFIRI regimen produced less toxicity than either the IFL regimen or an alternating irinotecan/bolus Mayo clinic fluorouracil/folinic acid schedule[54] (table VI). Three toxic deaths occurred, two in the IFL group and one in the irinotecan/Mayo Clinic group. In a randomised phase II trial in the second-line indication,[41] the three tested treatments (FOLFIRI, FOLFOX-4 and IROX) produced similar rates of neutropenia (grade 3 or 4, approximately 35%), whereas the rates of diarrhoea were much higher with IROX (33%) versus either FOLFIRI (6%) or FOLFOX-4 (3%). Only one toxic death occurred and it was in the FOLFOX-4 arm.

## 3. Benefit-Risk Evaluation

### 3.1 Summary of Benefits

Advanced CRC has a poor prognosis, with no long-term survival unless surgery can be performed. Fluorouracil-based chemotherapy, being the standard for many decades, can result in clinically meaningful gains in survival and QoL. Irinotecan has further improved these effects, as has been seen in several large randomised trials.

In addition to fluorouracil/folinic acid, irinotecan prolongs median survival by approximately 3 months (range 2.2–3.3 months in the trials), median time to tumour progression by approximately 2.5 months (2.3–2.7 months) and improves objective tumour response rates from approximately 20% to between 35% and 40%. The additive effects of irinotecan were independent of the fluorouracil/folinic acid schedule. The QoL scores of inter-

**Table V.** Incidence (%) of grade 3 or 4 adverse effects with fluorouracil (FU)/folinic acid (leucovorin) with or without irinotecan as first-line treatment in the pivotal phase III trials

| Adverse event | Saltz et al.[46] | | | Douillard et al.[45] | |
|---|---|---|---|---|---|
| | Bolus FU + no irinotecan (n = 219) | Bolus FU + irinotecan (n = 225) | Irinotecan alone (n = 223) | Bolus/infused FU + no irinotecan (n = 187) | Bolus/infused FU + irinotecan (n = 199) |
| Anaemia | | | | 2 | 3 |
| Neutropenia | 66 | 54 | 31 | 10 | 41 |
| Febrile neutropenia | 14 | 7 | 6 | 0 | 2 |
| Nausea | | | | 2 | 4 |
| Vomiting | 4 | 10 | 12 | 2 | 5 |
| Diarrhoea | 13 | 23 | 31 | 10 | 22 |
| Cholinergic-like syndrome | | | | 0 | 2 |
| Asthenia | | | | 1 | 7 |
| Mucositis | 17 | 2 | 2 | 2 | 3 |
| Anorexia | | | | 1 | 4 |
| Cutaneous signs | | | | 5 | 1 |
| Abdominal pain | | | | 1 | 2 |
| Non-neutropenic infection | | | | 2 | 5 |
| Drug-related deaths | 1 | 1 | 1 | 0 | 0.5 |

**Table VI.** Incidence (%) of grade 3 or 4 adverse effects occurring with combinations of fluorouracil/folinic acid (leucovorin), irinotecan and oxaliplatin as first-line treatment of metastatic colorectal cancer in randomised trials[a]

| Adverse event | Goldberg[51] | | | Tournigand[52] | | Bouzid[54] | | |
|---|---|---|---|---|---|---|---|---|
| | IFL[b] (n = 255) | FOLFOX-4[b] (n = 258) | IROX[b] (n = 256) | FOLFIRI[b] (n = 110) | FOLFOX-6[b] (n = 110) | IFL[b] (n = 51) | FOLFIRI[b] (n = 53) | Irinotecan/Mayo Clinic[c] (n = 50) |
| Neutropenia | 40 | 50 | 7 | 24 | 44 | 30 | 8 | 22 |
| Febrile neutropenia | 15 | 4 | 11 | 7 | 0 | 14 | 0 | 16 |
| Nausea | 16 | 6 | 19 | 13 | 3 | 6 | 6 | 8 |
| Vomiting | 14 | 3 | 22 | 10 | 3 | 8 | 8 | 8 |
| Diarrhoea | 28 | 12 | 24 | 14 | 11 | 18 | 15 | 22 |
| Paresthesias | 3 | 18 | 6 | 0 | 34 | 0 | 0 | 0 |
| Death within 60 days | 4.5 | 2.6 | 2.7 | 4 | 3 | 8 | 4 | 0 |

a Details of the treatment regimens are given in table III.

b Refer to table III for definitions.

c Folinic acid 20 mg/m$^2$ d 1–5, fluorouracil 425 mg/m$^2$ d 1–5 every 4 weeks.

viewed patients did not differ between treatment groups. This can be interpreted as indicating that the gain in survival was not accompanied by a worsening in QoL aspects during treatment.

After failure of fluorouracil/folinic acid therapy, single drug irinotecan prolongs median survival by approximately 2.5 months (2.3–2.7 months) relative to supportive or another (infused) fluorouracil/folinic acid regimen. In the trial comparing irinotecan with infused fluorouracil/folinic acid, median time to tumour progression was prolonged by 2.3 months. Also in these trials, the QoL-scores did not differ between groups. Since survival was prolonged, time to deterioration or symptom worsening was longer in irinotecan-treated patients.

### 3.2 Summary of Main Risks

Irinotecan has several acute adverse effects, both when given alone or in combination with fluorouracil/folinic acid or other cytotoxic drugs, that may negatively influence patient wellbeing. These are predominantly diarrhoea, nausea and vomiting, alopecia and acute cholinergic-like symptoms. In addition, irinotecan can cause haematological toxicity, predominantly neutropenia, which may be severe and life-threatening, particularly if combined with diarrhoea. The cholinergic-like syndrome can easily be prevented or treated. The other adverse effects can be diminished with adequate preventive actions, but most patients will still get some degree of toxicity with about 33% experiencing grade 3 or 4 toxicity (alopecia excluded). Patient characteristics are also important and toxicity will be seen both more frequently and will be of greater severity in poor performance status patients. However, after appropriate dose adjustments, if necessary, many patients can well tolerate irinotecan treatment for a prolonged time period. For irinotecan monotherapy, a lower initial dose, with dose escalation in the absence of any toxicity, appears to prevent some patients from experiencing the most severe toxicity. When irinotecan is combined with fluorouracil/folinic acid, the severity of the toxicity depends upon the fluorouracil/folinic acid schedule and an unacceptably high level, also including a few toxic deaths, has been seen with irinotecan combined with a weekly bolus fluorouracil/folinic acid regimen. However, minor adjustment of the irinotecan dose

appears to reduce toxicity to acceptable levels while maintaining efficacy, including when it is combined with a weekly bolus regimen.[62] Improved tolerability has also been seen when the fluorouracil dose is reduced,[47,61] but was potentially at the expense of reduced efficacy in one of the trials.[61]

### 3.3 Summary of Benefit and Risks

Irinotecan alone or combined with fluorouracil/folinic acid has contributed to a longer and better QoL for many patients with advanced CRC. However, the beneficial effects are not very pronounced and the toxicity may sometimes be substantial. Thus, the widespread use of irinotecan could at a glance be questioned. Yet, the oncological community has accepted irinotecan as a superior or otherwise relevant alternative to fluorouracil/folinic acid or best supportive care for treatment of metastatic CRC and, when the potential benefits and risks are described to patients and their relatives, the majority of them accept the treatment. Thus, the potential for further benefit after failing a fluorouracil-based regimen, is considered sufficiently large and the risks not too problematic to justify the therapy, given the dismal prognosis if patients are left untreated or only receive an alternative fluorouracil regimen. Patient characteristics are of great relevance when estimating the statistical risk of severe toxicity and some patients should not be treated.

In the first-line situation, several treatment options exist today for most patients. One of these is a combination of irinotecan with fluorouracil/folinic acid; the others are primarily oxaliplatin with fluorouracil/folinic acid or fluorouracil/folinic acid alone. The beneficial effects in terms of tumour response rates and time to treatment progression of combining fluorouracil with irinotecan or oxaliplatin are virtually identical and it is not possible to favour one over another. The toxicities differ markedly but, again, in the absence of specific contraindications it is not possible to recommend one over another. The irinotecan combination generally gives more acute toxicity, which is not always possible to predict for an individual patient, whereas oxaliplatin with fluorouracil/folinic acid gives less acute toxicity, but has a highly predictable late toxicity. Whether one toxicity is worse than the other remains unclear. Besides, since the regimen given first ultimately fails in most patients, second-line treatment is then required. Thus, the choice is whether one combination is preferred as first-line treatment and the other as second-line treatment or the other way round. Therefore, individual preferences are important.

In the future, molecular biomarkers[94] are likely to play an important role in the choice of drugs and appropriate sequence of various lines of treatment. The third alternative in previously untreated patients, i.e. to start with fluorouracil/folinic acid (or capecitabine[95]) alone, may also be relevant for some patients since it generally has less toxicity, although it more seldom induces tumour response compared with combination therapy. The time to tumour progression is also shorter and survival may be worse. These patients may then have the irinotecan/oxaliplatin combinations in second and third line. Whether first-line combination therapy is more beneficial to all patients is being tested in large randomised trials, one in the UK (FOCUS trial) and one in The Netherlands (CAIRO trial). The FOCUS trial, having included over 2000 patients, also compares irinotecan and oxaliplatin given as first-line treatment. This third alternative is not recommended in patients with a limited (but not resectable) tumour that may become resectable if tumour response is seen, simply because fewer patients will then respond.[3]

## 4. Conclusion

Irinotecan has antitumour activity in advanced CRC that is clinically relevant for some patients. The effects are well proven in randomised trials. Thus, irinotecan can, in some individuals, result in tumour regressions or disease stabilisations (therefore less tumour-related symptoms), longer time to disease progression and prolonged overall survival. Since the antitumour activity is comparably limited, irinotecan will be potentially beneficial in only a proportion (approximately 20–40%) of patients. In patients showing a tumour response to (the addition of) irinotecan, time to disease progression and overall survival may be prolonged by many months, whereas the life prospect is unaltered (potentially shortened if severe life-threatening toxicity occurs) in non-responding patients. The net effect of irinotecan is a prolongation of median survival by 2–3

months, regardless of whether it is given as a single agent in patients' refractory to standard fluorouracil/folinic acid or added to fluorouracil/folinic acid (or oral fluoropyrimidine) in previously untreated patients with metastatic CRC.

There is no consensus as to the minimal effect on survival or symptom relief that will justify offering patients a particular treatment, although the statements given in different official documents[15,16] indicate that the effects of irinotecan are just above or on the border of what can be accepted. The severity of the disease, as well as the risk of toxicity from the treatment, are also of great relevance when giving recommendations to large patient groups. Advanced CRC is a severe disease with a short median overall survival, thus comparably short prolongations of life may be very relevant. However, the risk of acute toxicity is comparably large. Taken together, irinotecan has been accepted by both patients and the medical profession, including this author, as a valuable contribution to the treatment of advanced CRC. However, appropriate patient selection, presently based mainly on patient characteristics and extent of tumour burden, is a must and some patients should not be treated with irinotecan. Hopefully, in the near future, much more sophisticated measures that are based upon pharmacogenetics and tumour biomarker profiling will be available.

Both irinotecan and oxaliplatin add toxicity and costs to the fluorouracil/folinic acid treatment regimen. Since the overall survival gain is probably small when using a combination regimen upfront, rather than a fluorouracil/folinic acid regimen alone, as first-line treatment, with any of the newer drugs later in the course, the regimen to choose must be selected individually and discussed with the patient. The importance of having access to all of the presently active cytotoxic drugs (fluorouracil/folinic acid, irinotecan and oxaliplatin) has recently been emphasised.[13] The availability (at reasonable cost) of several new agents, such as the monoclonal antibodies cetuximab and bevacizumab, which were recently found to have activity in advanced CRC, will also be of great relevance. These and other future targeted drugs, will result in major changes in the care and treatment of patient with advanced CRC. In the meantime, irinotecan has been,[96-98] and will likely continue to be, an important component in this rapid and fascinating development.

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