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FORTY YEARS ago the fluorinated form of the pyrimidine nucleobase uracil was described as an anticancer drug for the first time. It has since been used in the treatment of a variety of human cancers and is now an established drug alone or in combination with other agents for the treatment of gastrointestinal tract cancer, breast cancer and several squamous cell cancers. In the late 1970s new technical developments led to the elucidation of the mechanisms by which 5-fluorouracil (5-FU) exerts its effects. This opened ways to influence and improve these effects by the addition of modulating agents. In general, these agents are supposed to supply substrates or to inhibit competitively degrading enzymes. A number of substances have been shown to improve the effects of 5-FU on rodent and human tumour cell lines *in vitro*.

Clinical studies of the effect of modulating agents on 5-FU have almost exclusively been performed in colorectal cancer, probably because this entity was the only one where 5-FU has consistently been used as a single agent and no other drug showed sufficient efficacy to be used on a regular basis. Of all the agents studied, only two have been studied more extensively, namely methotrexate and folinic acid (citrovorum factor, leucovorin). In preclinical experiments it became apparent that for optimal modulation of 5-FU the dose/concentration of the modulator, duration of application/exposure and the sequence of administration are important variables. Unfortunately none of the preclinical models can predict the clinical situation. Thus, an empirical approach was required.

The modulation of 5-FU by methotrexate in human colorectal cancer has been extensively studied. A meta-analysis of all published phase III studies has been performed showing overall a small but significant survival benefit for those patients treated with sequential methotrexate and 5-FU versus those treated with 5-FU alone [1]. Nevertheless, this combination is not widely used, probably because its use is more cumbersome and the study of the North Central Cancer Treatment Group (NCCTG) has shown 5-FU modulated by folinic acid to be superior to sequential methotrexate/5-FU [2]. It must, however, be realised that the regimen of sequential methotrexate/5-FU used in the NCCTG study is considerably less dose intensive than the one used in other studies. The following will therefore concentrate on the question of whether the addition of folinic acid can improve the treatment results of 5-FU. Since there are no studies comparing 5-FU with the combination of 5-FU and folinic acid in the adjuvant situation, the discussion will concentrate on the treatment of advanced colorectal cancer.

Most of the phase II trials showing the combination of 5-FU and folinic acid to be effective in the treatment of advanced colorectal cancer concluded that phase III studies needed to be performed. Up to now more than 10 such studies have been reported. The reasons for this large number of studies are various: varying schedules of administration, varying doses of folinic acid, studies performed in different countries by different groups, unconvincing data from other studies. In principal, there were two different designs: one with the same dose and schedule of 5-FU on either treatment arm adding folinic acid to one treatment arm. The objective of these studies was to demonstrate the effect of the addition of folinic acid. They were not intended to test or compare equitoxic treatments. Thereby it was possible to show a modulating effect of folinic acid. This design has been used by most investigators and it clearly showed an advantage in terms of response rate, but also increased toxicity (Table 1). None of these studies showed a survival benefit for modulated 5-FU.

Table 1. *Phase III studies comparing* 5-*fluorouracil (*5-*FU)/folinic acid with* 5-*FU alone using same dose and schedule of* 5-*FU in both arms*

	Response rates (PR + CR%)		Grade 3 + 4 toxicity (%)		
Study	5-FU/folinic acid	5-FU	5-FU/folinic acid	5-FU	Survival benefit
Erlichman [3]	33	7	28*	21*	No§
Nobile [4]	23	8	20†	9†	No
Labianca [5]	21	10	18‡	10‡	No

*Neutropenia through cycles 1–6. Mucositis and gastrointestinal toxicity were highly significantly worse ($P < 0.00005$) with 5-FU/folinic acid in cycle 1. †Diarrhoea only ($P = 0.045$). ‡Percentage of patients experiencing toxicity, cumulative. §In the original paper a significant survival advantage was reported [3]. In a letter to the editor this was corrected [6]. PR, partial response; CR, complete response.

For the patients, the main objective, however, is improvement in therapeutic index. This can only be demonstrated, if treatments are compared that cause equivalent toxicity. Therefore, other studies have tested a different approach selecting a more dose-intensive regimen of 5-FU alone intending equitoxicity (Table 2).

The results shown in Tables 1 and 2 have also been described in the meta-analysis of a number of trials addressing the effectiveness of 5-FU/folinic acid as compared with 5-FU alone in advanced colorectal cancer [9]. Unfortunately the title of this publication '.....evidence in terms of response' is incorrect. Superiority in terms of response could only be shown for studies that used comparably low doses of 5-FU in the control arm. This was accompanied by more toxicity in the 5-FU/folinic acid treated patients. The response rates for the 5-FU/folinic acid combinations have varied within a wide range. For the so-called Mayo regimen the reported range is from 12.7% [10] to 22% [11] to 35% [12] to 43% [13]. The reason for this inconsistency could be patient selection, different methods in response evaluation and the presence or absence of extramural reviews.

Two studies tried to achieve equitoxicity by dose escalation. The study of Laufman and colleagues with a double-blind design using oral folinic acid or placebo, was successful in achieving some equitoxicity [14]. It clearly failed, however, to show a significant difference in terms of response rate, time to treatment failure, survival, quality of life measures and toxicity, except for duration of hospitalisation which was significantly longer for patients receiving folinic acid/5-FU. The Swiss study [11] used a more conventional, Mayo-type regimen with 5-FU and folinic acid given intravenously. It also requested dose escalations starting with an equimolar dose of 5-FU in both treatment arms. However, despite a significantly lower toxicity, the majority of the patients in the 5-FU alone arm had no dose escalation. This would explain why patients receiving 5-FU/folinic acid had a significantly higher response rate and a significantly longer survival.

It is remarkable that in addition to the intensity, the type of toxicity seen with 5-FU/folinic acid is somewhat different. If a Mayo-type regimen is used, mucositis and diarrhoea are the most common toxicities reported [15], whilst with 5-FU given alone as a rapid bolus injection haematotoxicity is more pronounced [13]. Therefore, it has been rather difficult to define equitoxicity. To just compare the percentage of patients experiencing, for example any grade 3 toxicity may be misleading, since for the actual patient grade 3 leucopenia is quite different from grade 3 stomatitis. Also, the quality of reporting of toxicity results may not be sufficient and the method of reporting toxicity has varied considerably between different reports.

There is only one published study that has shown a significant advantage of 5-FU/folinic acid over 5-FU alone in terms of survival [13]. This often-cited study has—besides other treatments—compared 5-FU 500 mg/m^2/day×5 every 5 weeks with folinic acid 20 mg/m^2/day immediately followed by 5-FU 425 mg/m^2/day for 5 consecutive days every 4 weeks×3, thereafter every 5 weeks. This is equivalent to a dose intensity for 5-FU of 500 mg/m^2/week versus 530 mg/m^2/week. Thus, in the control arm the 5-FU dose is rather high during the 5 days of treatment causing moderate toxicity and, therefore, probably some dose modification (not reported). Due to the long treatment intervals of 5 weeks, the overall intended dose intensity was considerably less than what can be achieved [7, 16]. In this study, a large portion of the patients had unmeasurable disease who seemed to benefit most in terms of survival advantage. In most other studies, only patients with measurable disease have been included. Therefore, the observed survival advantage may only be true for patients with unmeasurable disease.

The selection of patients for a study of chemotherapy in advanced colorectal cancer can have a considerable effect on outcome: patients with less advanced disease, better overall performance status and asymptomatic patients have a better chance of responding to whatever chemotherapy they are given.

Table 2. *Phase III studies comparing* 5-*fluorouracil (*5-*FU)/folinic acid with* 5-*FU alone using a higher dose intensity of* 5-*FU in the control arm*

	Response rates (PR + CR%)		Grade 3 + 4 toxicity (%)		
Study	5-FU/folinic acid	5-FU	5-FU/folinic acid	5-FU	Survival benefit
Valone [7]	19	17	10/22*	19/43*	No
Di Costanzo [8]	16	18	2/11†	2/5†	No

*Haematologic/non-haematologic. †Leucocytes/mucositis. PR, partial response; CR, complete response.

Table 3. Weekly 48 h infusion of 5-fluorouracil (5-FU) with or without folinic acid. Results of three consecutive phase II studies

5-FU dose intended g/m²/week	Folinic acid	No. of patients	Actual dose g/m²/week	RR (%)	Grade 3 + 4 toxicity (%) mucositis/diarrhoea
3.5	No	89	3	38.5	11/12
3	Yes	43	2.2	29	25/58
2	Yes	110	1.6	37.5	9/24

RR, response rate.

Table 4. Cost of treatment with 5-fluorouracil (5-FU) or folinic acid/5-FU based on full dose, body surface area of 1.7 m², 8 weeks' treatment period and least expensive drug supplier

Regimen	5-FU dose	Folinic acid dose	SFR
Mayo type [11]	400 mg/m²/day×5 every 4 weeks	20 mg/m²/day×5 every 4 weeks	475.00
Single agent	400 mg/m²/day×5 every 4 weeks	–	120.00
Spanish [18]	1.6 g/m²/48 h every week	60 mg every 6 h×8 every week	1799.00
Spanish	3 g/m²/48 h every week	–	350.00

SFR, Swiss francs.

Many years ago it was shown that there is a steep dose–response (and dose–toxicity) curve for 5-FU in the treatment of colorectal cancer [17]. In my opinion, dose escalation is not an ideal way to test the dose–response effect in the individual patient, since resistance is likely to be induced early. It could, therefore, be speculated that it could be more advantageous to start with a higher dose intensity of 5-FU and de-escalate in case of toxicity.

While there has been some debate as to which regimen of 5-FU is superior, in principal three different regimens have been used for the combination with folinic acid:

- 5-FU bolus daily×5 every 4–5 weeks, single dose 370–425 mg/m²;
- 5-FU bolus weekly, single dose 500 mg/m²;
- 5-FU 24 h continuous infusion weekly, single dose 2600 mg/m².

The first two have been compared in a randomised study, where they were found to be approximately equally effective, with a small advantage of the daily×5 regimen in terms of toxicity [12]. The latter schedule, which has achieved interesting response and survival data in phase II studies, has not yet been prospectively compared with the other regimens nor with 5-FU alone. There is, however, a report from a Spanish group which has evaluated a similar regimen with and without folinic acid in three consecutive phase II studies (Table 3) [18]. These results strongly suggest that the addition of folinic acid to this type of 5-FU regimen does not improve therapeutic index.

It is interesting to note that folinic acid has been added to 5-FU in the treatment of other cancers as well, although no formal studies have been carried out to determine whether this would add more than cost and toxicity. Only recently, a small study was reported in head and neck cancer indicating a disadvantage with the addition of folinic acid to 5-FU [19].

It is likely that there is yet another reason why 5-FU given as a single agent seems to be inferior when compared with 5-FU/folinic acid. In a recent editorial I speculated about the influence of the actual duration of a 'bolus' injection on treatment outcome [20]. It has now been shown that the duration of a 'bolus' injection of 5-FU indeed matters. Patients receiving 5-FU within 2–4 min had a significantly better response rate as compared with patients receiving the same dose within 10–20 min [21]. Since in many institutions people use piggy bags for the application of 5-FU it is likely that the majority of patients have received 5-FU over more than 10–15 min. In this situation, more time would be available for 5-FU to be degraded by the enzyme dihydropyrimidine dehydrogenase, whereas with a real bolus injection more 5-FU would be available to be anabolised to an active metabolite due to saturation of the degrading enzyme.

In summary, there are no convincing data that the addition of folinic acid to 5-FU has a clear beneficial effect. Even if it had a small effect, what would be the cost? Table 4 compares the cost just for the drugs and shows that the addition of folinic acid adds considerable cost, which in my mind is not justified by the available data, keeping in mind the limited amount of money for health care.

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DESPITE THE availability of 5-fluorouracil (5-FU) for four decades, the issues of optimal scheduling and the role of biochemical modulation of 5-FU remain controversial. As 5-FU has been the most active drug available for the treatment of colorectal cancer until recently, the potential enhancement of the efficacy of 5-FU by biochemical modulation and/or manipulation of the schedule has remained a major clinical research priority. Sobrero and Herrmann have presented opposing views on the impact of biochemical modulation of 5-FU [1, 2]. Both authors have focused on colorectal cancer as there is insufficient evidence to draw any conclusions in other tumour types.

In the adjuvant setting, there has not been any direct comparison of unmodulated and modulated 5-FU. However, unmodulated 5-FU has not been demonstrated to be an effective adjuvant treatment, perhaps related to the relative dose intensity of the 5-FU regimens used [3]. In contrast, 5-FU and folinic acid improves survival in stage III carcinoma of the colon and 5-FU combined with folinic acid or levamisole has become standard adjuvant therapy for patients with stage III disease [4, 5].

It is in the advanced disease setting that the arguments about the benefits of modulated 5-FU compared with unmodulated 5-FU have continued over the last 10 years. As both authors have pointed out, the controversy revolves around the benefits of adding either folinic acid or methotrexate to 5-FU as the addition of interferon has not been shown to be beneficial [6]. We propose to concentrate primarily on the role of folinic acid and 5-FU, as this combination, rather than 5-FU and methotrexate, has been adopted as standard chemotherapy for advanced colorectal cancer by many centres around the world. Nevertheless, a meta-analysis found that the addition of methotrexate results in an improved response rate and a small improvement in survival [7], although interpretation of these trials is confounded by the use of different regimens with variable intervals between the two drugs and the use of folinic acid for methotrexate rescue.

Randomised trials have primarily addressed the role of folinic acid in the context of bolus schedules of 5-FU. A meta-analysis found improved response rates without any improvement in survival when 5-FU and folinic acid combinations were compared with 5-FU alone [8]. The meta-analysis included different schedules and doses of both 5-FU and folinic acid. The North Central Cancer Treatment Group (NCCTG) trial, which was the only trial at that time to have demonstrated a survival advantage for the combination, was not included in the analysis, although it was estimated that its inclusion would not have altered the conclusions of the statistical overview [9]. The recently published results of a large Swiss Group for Clinical Cancer Research (SAKK) trial

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