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# Current Controversies in Cancer

# Does Biomodulation of 5-Fluorouracil Improve Results?

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### INTRODUCTION

THE TITLE of this controversy is very broad and somewhat ambiguous. Clarifications and restrictions are needed.

*'Biomodulation'*

'Biomodulation' is a non-classical word and clearly means more than simple biochemical modulation. Such is the case for 5-fluorouracil (5-FU) modulation by interferon, IL-2, levamisol and others. This paper will be limited to the classical biochemical modulation of 5-FU by leucovorin (LV) and methotrexate (MTX) and to modulation by levamisol. The data regarding interferon are clearly negative and those on other modulators such as phosphon-acetyl-L-aspartate, azidothymidine, thymidine, uridine and others, are not sufficient for conclusions on efficacy.

*'5-FU'*

'5-FU' is not so ambiguous, but a crucial distinction must be made between 5-FU bolus and 5-FU continuous infusion (CI) . As we have recently pointed out [1] the two modalities of administration account for different spectra of toxicity, dose limiting toxicity, maximum tolerated dose, dose per cycle, dose intensity achievable, threshold dose for clinical activity and the range of useful doses for clinical activity. These differences are in keeping with the hypothesis that, depending on the dose and schedule, 5-FU has different mechanisms of action [2, 3]. When talking about clinical efficacy, I think that convincing evidence is available for the value of 'biomodulation' of bolus 5-FU, whereas not enough data are available for 'biomodulation' of CI 5-FU. In this regard, the definition of CI 5-FU is therefore very important. Anything longer than a 3 h infusion (and probably even shorter infusion times) should be regarded as 'a kind of CI' [1]. Thus, the analysis will be limited to true bolus 5-FU with or without modulation.

*'Improve results'*

Which disease, which setting, which endpoint? Again not enough data are available on breast, gastric and head and neck cancer. Therefore, only the data regarding colorectal cancer will be considered here. As to the setting, only colon cancer will be considered for the adjuvant setting. Both colon and rectal primaries will be considered together when talking of advanced disease.

### BIOMODULATION OF 5-FU IMPROVES RESULTS IN THE ADJUVANT SETTING

Although no direct comparison of modulated versus unmodulated bolus 5-FU is available, there are three pieces of evidence that strongly support this view:

(1) 5-FU modulated by levamisole is superior to control whilst 5-FU alone is not;
(2) 5-FU modulated by LV is superior to control whilst 5-FU alone is not;
(3) 5-FU + LV is preferable to 5-FU + levamisole.

(1) The single most important advancement in clinical oncology in the last 10 years has been the recognition that adjuvant therapy of Dukes' C colon cancer with 5-FU + levamisole significantly reduces the risk of recurrence and death from this disease. This benefit is in the order of 30% in terms of relative risk, that translates into approximately 10% more patients alive without recurrence 9 years after surgery [4]. Although the mechanism of action of the combination 5-FU + levamisole is not understood, the superiority over untreated controls remains. In contrast, none of the 16 trials of chemotherapy versus control conducted in the previous 30 years has ever shown significant survival advantage. In addition, the meta-analysis of all the adjuvant studies showed a 5 year survival benefit of 5-FU-based chemotherapy of 2.3%. If the meta-analysis is restricted to those trials where patients received at least 1 year of 5-FU treatment, the 5 year survival benefit is 3.4%, but still non-significant [5].
(2) The data on adjuvant 5-FU + LV versus control or MOF are quite straightforward: all four studies on a

total of 3107 patients are positive in terms of recurrence free survival and all except the smallest one are positive in terms of survival as well. This is reassuring since 5-FU + LV is a 'more rationally based biochemical modulation' of 5-FU than 5-FU + levamisole and 5-FU + LV works in the advanced setting of colorectal cancer whilst 5-FU + levamisole does not. As such, 5-FU + LV should be superior to 5-FU + levamisole. And this is indeed the case.

(3) 5-FU + LV is preferable to 5-FU + levamisole for a variety of reasons. The direct comparison 5-FU + LV versus 5-FU + levamisole has been studied in three trials on approximately 6700 patients. One study showed superiority both in terms of survival and in terms of disease free survival [6], the other two showed equivalence [7, 8]. In these studies, the duration of 5-FU + LV treatment is shorter than that of 5-FU + levamisole. The NSABP trial C-04 showed the superiority of 8 months of 5-FU + LV versus 12 months of 5-FU + levamisole [6]. The 'duration' trial [7] showed equivalence between 12 months of 5-FU + levamisole and 6 or 12 months of 5-FU + LV, suggesting that nothing is gained by prolonging 5-FU + LV treatment for 1 year. However, the same trial also showed that 6 months of 5-FU + levamisole is inferior to 12 months of 5-FU + levamisole and to 6 or 12 months of 5-FU + LV. This is also indirect proof of the superiority of 5-FU + LV over 5-FU + levamisole. Finally the third North American trial [8] also showed equivalence between 5-FU + levamisole and two schedules of 5-FU + LV, but the comparison was made between 12 months of 5-FU + levamisole and 6 months of 5-FU + LV again.

Similar observations may be made as regards the total dose of 5-FU compared in these studies: 23.8 g/m$^2$ for 5-FU + levamisole, 18 g/m$^2$ for 5-FU + LV in the RPMI weekly regimen and 12 g/m$^2$ in the 5-FU + LV Mayo monthly regimen.

5-FU + LV may work in Dukes' B2 patients as well [9] whilst 5-FU + levamisole does not.

5-FU + LV may not be less toxic than 5-FU + levamisole: in fact although 5-FU + levamisole produced no more than 4% grade 3–4 toxicity in the intergroup trial, that figure for the same regimen was 28% in the NSABP trial; similarly while the NSABP study reported 35% severe toxicity with weekly 5-FU + LV, the IMPACT study reported only a 5% incidence of such toxicity. The degree of variation is similar for the two drug combination when used in the adjuvant setting.

Finally, and least important from a clinical viewpoint, 5-FU + LV has a rationale, whilst 5-FU + levamisole has not!

## BIOMODULATION OF 5-FU WORKS IN THE ADVANCED SETTING

As in many other neoplasms, the efficacy of colorectal cancer chemotherapy is a function of tumour mass. The currently available literature suggests that even small improvements in the advanced setting may turn into major additional gain in the adjuvant setting. When the tumour is at the microscopic level (the adjuvant setting) some benefit is afforded even by unmodulated 5-FU (the non-significant data of the meta-analysis) and the benefit becomes highly significant when 5-FU is modulated. But when the disease is advanced, clearly measurable or even massive, the clinical benefit is marginal. Great caution must be exercised in this setting. The game is going to be lost anyway and the intent of any clinical intervention can only be palliative. The major issue here is whether the patient needs treatment or not. A 75 year old, symptomatic patient with a performance status of 2, extensive disease, baseline LDH of 2000 units and baseline white cells of 15 000 is never going to benefit from any available regimen, whereas as tumour bulk decreases the benefit may be substantial. Thus, aside from the immediate benefit that the patient with metastatic cancer may get from chemotherapy, the results of therapeutic trials against the advanced disease remain very important in the light of the potentially amplified effect that might be obtained in the adjuvant setting.

Once it is decided that a patient needs chemotherapy for advanced colorectal cancer, the choice of the 'best' regimen remains a problem. I think that unmodulated bolus 5-FU is not appropriate treatment for these patients. Conversely, unmodulated CI 5-FU may be a valid option, but , if bolus administration is the preferred way of administering the fluoropyrimidine, then, modulation with either LV or MTX is needed. This approach is derived from several lines of evidence.

- There are individual large-scale, well-conducted randomised comparisons showing the superiority of modulated versus unmodulated bolus 5-FU.
- The two meta-analyses on 5-FU + LV and MTX 5-FU versus 5-FU alone showed a doubling of the response rate with a small non-significant prolongation of survival for 5-FU + LV and a small, but significant prolongation of survival for MTX 5-FU versus 5-FU alone [10, 11]. One may argue that since the time of the meta-analyses other randomised trials have been published questioning the value of biochemical modulation [12, 13]. However, if we consider all randomised trials of bolus 5-FU + LV versus unmodulated bolus 5-FU with more than 50 patients per arm, there are 11 trials, and in none of these trials was 5-FU alone statistically superior to 5-FU + LV. Conversely 5-FU + LV produced statistically higher response rates in 7/11 studies, statistically longer time to treatment failure in 4/11 studies, statistically longer survivals in 4/11 studies and statistically superior palliative effects in 3/4 trials where these endpoints were measured. Although the superiority is far from being absolute, it would be hard not to choose the modulated option, unless toxicity was significantly worse.
- When toxicity was analysed in these 11 trials, the following median percentages of grade 3–4 were obtained for unmodulated and LV modulated 5-FU: stomatitis: 13% for 5-FU alone, 20% for the monthly 5-FU + LV schedule, 9% for the weekly 5-FU + LV schedule; diarrhoea: 10% for 5-FU alone, 10% for the monthly 5-FU + LV schedule, 24% for the weekly 5-FU + LV schedule; leucopenia: 16% for 5-FU alone, 7% for the monthly 5-FU + LV schedule, and 8% for the weekly 5-FU + LV schedule.
- The contention that unmodulated bolus 5-FU regimens could have been intensified in those studies showing superiority of the modulated treatment can easily be challenged by the observation that in these studies leucopenia was already at an almost prohibitive level.

- Aside from the classical observation on patient selection, the Lauffman trial [12] suggesting inactivity of modulation can be challenged: it is true that dose escalation to reach equal toxicity was planned, but that study allowed waiting until patients became symptomatic for starting treatment. This is known to reduce substantially the clinical benefit of chemotherapy. In addition, the often quoted SWOG trial [13] is the only one out of 23 randomised comparisons published in the last 12 years showing a response rate to unmodulated bolus 5-FU greater than 20% [1].

Sequential MTX→5-FU has been the subject of fewer clinical studies than 5-FU + LV. The meta-analysis has shown significant benefit of this combination over 5-FU alone, both in terms of response rate and survival, but MTX→5-FU has not been pursued actively by many leading cancer centres. None of the studies included in the meta-analysis employed the same regimen! The Mayo Clinic dismissed this combination in 1991 after using too short an interval between the two antimetabolites (3 h only); MTX→5-FU was neither among the seven arms of the recent SWOG screening trial nor among the five arms of the ECOG study. Perhaps the scarce popularity of this regimen is due to the lack of appreciation for an appropriate interval between MTX and 5-FU administration (24 h) and also to the criticism that LV, used as MTX rescue, may actually work to modulate 5-FU. The different activities between the randomised trials employing shorter or longer than a 4 h interval between the antifolate and the fluoropyrimidine are well known [1].

A final consideration for modulation of 5-FU with LV concerns the time factor. It is more philosophical than scientific but still worth remembering. It usually takes 2–3 years for a regimen's popularity to peak, then within the next 2–3 years there is a rebound nadir and another 2–3 years are needed to establish the real value of that new combination. Good examples of this are MOF, MOF Strep and 5-FU–interferon. Now let us consider 5-FU + LV. Born in the laboratory in 1978, went into phase I in 1980, phase II in 1983 and phase III in 1985; then went into the adjuvant setting and now it has a strong established role. Eighteen years and it is still alive and well!

## ANY ROOM FOR IMPROVEMENT? YES: HYBRID REGIMENS AND SCHEDULE SPECIFIC MODULATION

If it is true that 5-FU behaves as two different drugs according to the schedule of administration, maximal enhancement of bolus 5-FU is more likely to be obtained with drugs that enhance the RNA effect of this fluoropyrimidine, such as MTX and PALA, than with LV. LV represents a selective method to enhance the TS inhibition. Based upon our *in vitro* studies and others', the following can be predicted in the clinic: (1) CI 5-FU plus LV should be superior to bolus 5-FU plus LV; (2) bolus MTX→ 5-FU should be superior to CI 5-FU modulated by the antifolate; (3) some activity should still be present in either regimen in patients failing the other one, as discussed for unmodulated 5-FU; (4) bolus 5-FU could be combined with CI 5-FU to produce hybrid regimens; (5) hybrid regimens containing schedule selective biochemical modulation of 5-FU bolus and CI should produce the highest activity in advanced colorectal cancer. A recent review discusses these predictions [1]. The last two will be mentioned here.

The 'De Gramont schedule' is very popular in northern Europe and the results are very promising. The randomised comparison with bolus 5-FU + LV has shown a significantly higher response rate and longer time to progression, although survival was not significantly longer [14]. It is an example of a hybrid regimen. Biochemical modulation of this regimen is not 'schedule specific' in that high dose LV is intended to modulate bolus and CI 5-FU. However, modulated bolus 5-FU plays the major part in this programme as its dose intensity is more than adequate, as compared with a very low dose intensity for the CI part . Hence, there is room for improvement of this regimen.

Based upon our hypothesis that biochemical modulation should be schedule specific, we have developed a different hybrid regimen alternating two biweekly cycles of 5-FU bolus, preceeded by (24 h interval) MTX with a 3 week CI of 5-FU modulated by low dose 6-S-LV. A 48% response rate, a median progression free survival and overall survival of 9.6 and 20.8 months, respectively, were obtained in the first phase II study [15] and the data from a large randomised comparison between this regimen and bolus MTX→5-FU are awaiting maturation.

## CONCLUSIONS

How should we treat our patients? Enrolment of them into well-designed randomised clinical trials should be highest on our list. The ongoing randomised studies may soon demonstrate the value of adding the new active agents CPT-II and/or oxaliplatin to the 5-FU-based regimens. But what should the reference arm be in these trials and what about the treatment outside clinical trials?

For the adjuvant setting, either the weekly regimen of 5-FU plus high dose LV for four cycles (8 months) or the monthly regimen of 5-FU plus low or high dose LV for six cycles should be considered 'standard'. It would be hard to suggest unmodulated bolus 5-FU alone.

For the advanced setting, once again the crucial issue is deciding if the patient is a candidate for chemotherapy, i.e. may benefit from it. If so, modulated bolus 5-FU or CI 5-FU with or without modulation should be used. Again I find it hard to suggest unmodulated bolus 5-FU alone.

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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.