Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 1919–1920, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00578-1

Editorial

Thymidylate Synthase Inhibition, a Dead End?

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While in the 1970s, chemotherapy studies in colorectal cancer seemed to be rather uninspired, the advent of biochemical modulation of 5-fluorouracil (5-FU) has changed this considerably. Whereas before, most patients, particularly in Europe, did not receive chemotherapy at all for advanced colorectal cancer, now the combination of 5-FU and folinic acid (FA) has advanced to standard treatment in many institutions. What was the basis for this?

In the late 1980s, several randomised studies were published showing a significant advantage of 5-FU plus FA over 5-FU alone in terms of response rate and some even in terms of survival[1]. Was this enough evidence to show that 5-FU can be modulated by FA? By adding FA to the same dose of 5-FU in the same schedule, more responses, more toxicity and perhaps even longer survival are obtained, which would indicate that FA does modulate 5FU.

However, the evidence to show that 5-FU plus FA is superior to 5-FU alone is insufficient. In almost all trials, patients in the 5-FU alone arm received inadequate treatment, which can be seen when toxicity is examined. Those trials using a higher 5-FU dose in the control arm showed no advantage for the 5-FU plus FA combination[1]. Admittedly, since the type of toxicity is different between 5-FU alone and 5-FU plus FA, it is difficult to establish an equitoxic dose. Perhaps the best of many 5-FU plus FA combinations in terms of response rate and yet the least expensive one was reported by the NCCTG-Mayo Group[2]. It originally produced a response rate of 43% (i.e. 16 of 37 patients with measurable disease) (99% confidence interval 23–65%) and a significantly longer survival as compared to 5-FU alone (limited to patients with non-measurable disease). In a follow-up study, 36 of 102 patients (35%, 99% confidence interval 23–48%) with measurable disease responded to the same regimen[3].

The results of the 5-FU plus FA combination, whose target is thymidylate synthase (TS), has triggered the development of specific TS inhibitors. The first one on the market is likely to be Tomudex (ZD1694), and the results of a phase III study, comparing Tomudex to the Mayo type 5-FU plus FA regimen, are reported in this issue (pages). With the help of the company developing this drug, Cunningham and associates have been able to recruit more than 400 patients within 8 months from more than 60 centres in 15 countries on three continents. Although the results are somewhat preliminary, they may be disappointing to many.

The objective response rates of both 5-FU plus FA (13%) and Tomudex (20%) were rather low. One reason might be that response evaluations were performed at 12 week intervals only. While overlooking a few responses may not be a major problem, failing to detect progressive disease within 6 or 8 weeks and therefore subjecting patients to unnecessary toxic treatment is a greater concern. I doubt that many oncologists in Europe close their eyes for 12 weeks. Doing a chest X-ray and/or an abdominal ultrasound every 6 or 8 weeks is likely to be less expensive than one or two more rounds of unnecessary chemotherapy.

Another possible reason for the low response is differences in patient characteristics. For example, in the Mayo study, 31% of the patients gained weight on 5-FU plus FA compared with only 12% in the present study. Unfortunately, most reports lack important patient characteristics which, if present, would make the results more easily comparable. In addition, auditing of source data by study monitors, as in the Cunningham study, may decrease response data. A company independent review panel would have been even better.

Time to progression and survival were not significantly different. In fact, median survival for both treatments appeared to be below 12 months which is similar to the Mayo data for patients with measurable disease[2]. However, this must await further follow-up. In addition, quality of life data, which are supposed to measure the patients perception of toxicity and treatment benefit, were not significantly different.

The toxicity data were somewhat better with Tomudex, with a significant reduction in the incidence of mucositis and leucopenia in Tomudex treated patients compared with 5-FU plus FA treated patients. The reduction in mucositis is the most important, since the more severe leucopenia in 5-FU plus FA treated patients was apparently not accompanied by increases in fever or infection. In addition, the frequency could probably be reduced by identifying patients with progressive disease earlier.

Finally, economical aspects play an ever more important role in medicine. While to give a drug such as Tomudex, once every

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Received 17 Oct. 1995; accepted 18 Oct. 1995.

3 weeks is less expensive than to give it on 5 days every 4 or 5 weeks, with the current prices of new drugs, it is unlikely that Tomudex treatment will be less expensive than 5-FU plus FA. Clearly, 5-FU plus FA does not require hospitalisation and days 2–5 can easily be administered by a family physician.

Thus, Tomudex may (or may not) be a little better than 5-FU plus FA in terms of tumour response. However, in terms of toxicity and handling, the data are not sufficient to indicate that Tomudex can replace 5-FU plus FA or for that matter 5-FU as single agent in the treatment of advanced measurable colorectal cancer.

This does not mean that we have made no progress with the cytotoxic treatment of colorectal cancer within the last 10 years. On the contrary, it is now known that chemotherapy prolongs survival of patients with advanced colorectal cancer when compared to best supportive care[5] and that patients benefit from early treatment[6]. In addition, expression of TS predicts for response/resistance to 5-FU based chemotherapy[7], and drugs with novel mechanisms are being introduced (e.g. Topo-I inhibitors).

Metastatic colorectal cancer is not a homogenous disease. We need to select those patients who are most likely to benefit from chemotherapy, thereby sparing some patients its unpleasant side-effects.

Perfecting the inhibition of TS is not the future, neither with further modulation of 5-FU nor with specific TS inhibitors. While normal tissues eventually need some functional TS, many colorectal cancers need less. In my opinion, persuing TS inhibition alone is a dead end. However, results of combinations of TS inhibitors with other drugs effective in colorectal cancer are eagerly awaited.

1. Advanced Colorectal Cancer Metaanalysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
2. Poon MA, O'Connell MJ, Moertel GG, *et al.* Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989, **7**, 1407–1418.
3. Buroker TR, O'Connell MJ, Wieand HS, *et al.* Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994, **12**, 14–20.
4. Cunningham D, Zalcberg JR, Räth U, *et al.* "Tomudex" (ZD1694): Results of a randomised trial in advanced colorectal cancer demonstrate efficacy and reduced mucositis and leucopenia. *Eur J Cancer* 1995, **31A**, *XX–YY*.
5. Scheithauer W, Rosen H, Kornek GV, *et al.* Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
6. The Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Expectancy of primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992, **10**, 904–911.
7. Leichman CG, Lenz HJ, Leichman L, *et al.* Quantitation of intratumoral thymidylate synthase expression predicts for disseminated colorectal cancer resistance to protracted infusion 5-fluorouracil and weekly leucovorin. Proc Am Soc Clin Oncol 1994, **13**, 592.