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5-FLUOROURACIL (5-FU) was synthesised in 1957. Since the early data suggesting its activity in colorectal cancer, medical oncologists have never challenged its utility. The "proof" of its activity, as recalled by Blijham (see pages 815–817), lies in response rates that varied from 0% to 87%. Oncologists felt that response, as defined by shrinkage of the tumour by at least 50%, would also generate a survival benefit. Indeed, comparing survival curves of responders to non-responders showed a convincing advantage for responders. However, as the comparison of survival by response was not accepted by leading cancer journals, all the published studies have been negative.

Who was right? It is generally considered that survival of responders could be attributed to other prognostic factors, mainly the performance status, which is a highly significant predictor of both therapeutic response and overall survival in patients with advanced colorectal cancer [2, 3]. Response would, therefore, reflect inherent survival advantage, regardless of treatment. The subject by itself is a matter of controversy [4]. However, using data from randomised trials in advanced colorectal cancer, it has recently been suggested that response is a potent and independent prognostic factor of survival in that disease [5] and that response can be used as a surrogate marker of survival [6].

The oncologists had good intuition: response is a good surrogate for survival and should remain the cornerstone of activity. What was obvious for oncologists was not for non-oncologists, who considered that the benefit, if any, was too small to overcome the disadvantage(s) of chemotherapy.

The reasons why it took more than 30 years to compare patients receiving chemotherapy to patients who did not, probably reflect the trust oncologists had in their intuition. The results are straightforward and hardly require *P* values to be interpreted. The effect of treatment is globally noticeable on the whole group of patients and the benefit translates in a doubling of the survival time and an improved quality of life [7]. Moreover, the patients who received chemotherapy when they were asymptomatic had twice the survival of patients treated when they had symptoms [8]. These data should convince any physician of the validity of chemotherapy in advanced disease.

The considerable amount of data generated in advanced colorectal cancer show that various schedules and doses of 5-FU allow prolongation of survival and improvement of quality of life. Can these results, obtained in clinical trials, be transposed into daily practice? This is far from settled.

The proportion of patients with advanced colorectal cancer being treated with chemotherapy is rather small in most European countries and even in the U.S.A. The Colorectal Care Pathway Review has made enquiries in various European countries and in the U.S.A. A total of 636 professionals dealing with colorectal cancer were asked why patients with colorectal cancer were not referred to. For patients with advanced disease, the reasons for surgeons not referring patients with advanced disease for further treatment were: patient's request (14%), no benefit (14%), patient too sick (13%), geography (10%), poor funding (10%). Cancer remains an unmentionable disease. The

Colorectal Care Pathway indicates that only 20% of the patients are very aware of the disease and its implications, 40% are partly aware, 40% are not [9]. The diagnosis remains concealed, the physician and the family build up a wall of lies around the patient making access to information extremely difficult. The patient himself is involved in a cultural net where silence is the rule. Even if he has some suspicion, the fear of words, the fear of truth, the fear of being confronted with real life will keep him far from oncology medical care. If he finally seeks treatment, it is often at a more advanced stage when pain, weight loss or ascites make any intervention useless. Non-oncologists, general practitioners, internists and surgeons perpetuate that situation. Only patients who are well informed, supported by careful and convinced physicians will effectively take advantage of the available treatments. Based upon the Colorectal Care Pathway, this would not represent more than 20% of the patients [9].

Among the reasons put forward for not giving chemotherapy, the lack of clinically significant benefit is one of the most quoted and, even if some benefit is recognised, many would consider that increasing survival by 6 months is insufficient and does not counterbalance the inconveniences related to the treatment. Cancer patients' attitudes to chemotherapy have been compared with those of doctors, nurses and healthy controls. Patients were significantly more willing than controls and professionals to accept intensive chemotherapy treatments for a potentially small benefit. Moreover, patients under 40 years of age demanded insignificant benefits even in the palliative setting [10].

A major problem in Europe might be the fact that oncology is not a uniformly recognised speciality. The patient with colorectal cancer in the hands of an internist not trained in oncology will probably be undertreated, the main objective being to avoid toxicity and, seemingly, preserve the patient's quality of life. If, indeed, the side-effects of chemotherapy can reduce the patient's quality of life, this is insignificant compared to the troubles induced by the disease itself which sooner or later will emerge. The untreated patient will have a shorter survival and the symptoms of the disease will emerge more rapidly [8]. Data suggest that chronomodulated 5-FU, folinic acid and oxaliplatin allow some patients to be re-operated upon with curative intent, for their liver metastases [11]. Moreover, second-line treatment using CPT-11 or oxaliplatin suggest that the survival of patients with advanced disease could be prolonged [12, 13].

The question of whether to treat or not to treat is obsolete. Nowadays, the question is how to provide adequate treatment to the affected persons. The answer lies in the education of physicians in charge of the patients and of the population. Although advanced colorectal cancer cannot be cured, death can be temporarily postponed thanks to treatments that bear the potential of reducing the severity of the symptoms and of prolonging survival. Respect for patients would require that each patient with advanced colorectal cancer should be informed of all treatment possibilities. The physician should let the patient decide whether an additional 3 months survival justifies being submitted to an aggressive treatment.

The benefits obtained by administering chemotherapy for a metastatic colorectal cancer are nevertheless extremely weak and definitely insufficient. How could we, at least, identify those patients who will not receive any advantage from treatment, so avoiding the administration of useless (and potentially toxic) treatments? Performance status is a useful variable but unable to identify all patients who will not benefit from chemotherapy. Other variables should be investigated such as the percentage of liver involvement [14] and the baseline value of lactate dehydrogenase (LDH) or white blood cell count (WBC) [15]. Molecular biology could also predict response and survival in patients with malignancy. High levels of *TP53* mutations have been associated with poorer survival and chemoresistance [16]. A huge amount of work remains to be done in this field.

How can we expand the benefit of treatment and gain more high-quality survival? Uncontrolled studies suggest that patients receiving second-line chemotherapy may show an objective response or a stable disease with prolonged survival. Randomised studies comparing patients receiving CPT-11 to patients receiving no chemotherapy or a "best second-line" 5-FU containing regimen are underway and should help us to identify new strategies for treating our patients.

Active treatments are available. New promising agents are upcoming. Clinical research in the field of colorectal cancer remains, more than ever, mandatory. It represents the only chance for progress, it is also the best chance for our patients to receive the best available care.

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