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INTRODUCTION

COLORECTAL CANCER is one of the most common neoplastic diseases and is second only to lung carcinoma as a cause of death from cancer. Although most patients are surgically resected, almost half die of the disease with more than 70% of relapses involving a distant site. After many years of disappointing results, adjuvant chemotherapy has now a definite role in this disease: several studies have demonstrated in Dukes' C, and more recently Dukes' B, patients a significant benefit from 5-fluorouracil (5-FU) in association with levamisole or folinic acid (FA) or both [1–3]. Also, intraportal chemotherapy seems to be promising when delivered after resection of the primary [4].

In contrast with the positive results achieved in the adjuvant setting, the role of chemotherapy in advanced disease is much less clear. Only a few studies have addressed the question of whether these patients should be treated with cytostatics or best supportive care only.

- An Austrian trial compared 24 patients randomised to chemotherapy with 12 randomised to supportive treatment and demonstrated a longer median survival (11 versus 5 months, $P < 0.006$) and a suggestion of better palliation in symptomatic patients in the treated group [5].
- In the U.K., 100 patients with liver metastases were randomised between intra-arterial FUDR and best supportive care: the patients receiving chemotherapy experienced a significantly better survival (14 versus 7 months, $P < 0.05$) [6].
- A Scandinavian study of 183 patients evaluated the role of immediate chemotherapy in comparison to a wait-and-see policy (in the latter group, cytotoxic treatment was allowed when symptoms developed) and reported a 5-month median survival increase and a symptom-free period of 10 compared to 2 months when immediate chemotherapy was administered [7].

Although all these studies support the concept of an active treatment of patients affected with advanced colorectal cancer, in clinical practice there is no definite consensus about the value of chemotherapy in this setting. Even after resection of the primary, many patients are not referred for chemotherapy: a survey in U.K. found that only 60% of medical oncologists were giving chemotherapy to Dukes' C tumours [8]. In advanced disease, the attitude of many clinicians is even more pessimistic, as indicated by a recent study performed by the International Working Group in Colorectal Cancer [9]. A "Colorectal Cancer Care Pathway Review" was designed in order to assess how advanced colorectal cancer is currently managed and to provide the basis for development of a model for best practice in the management of this common disease. The survey was performed at several institutions (general hospitals and oncology centres) in France, Germany, Italy, U.K. and U.S.A., interviewing 422 professionals (surgeons, medical oncologists, radiotherapists and nurses) about referral and treatment patterns of colorectal cancer. Although the vast majority of clinicians recognised the importance of a multidisciplinary work, they considered referral patterns to be variable and believed that up to 40% of patients are not being appropriately referred for treatment. Among the several reasons for this negative behaviour (lack of geographic accessibility, request of patients and their relatives, difficult funding, etc.), one important issue could be that many people did not perceive a real benefit for the patients treated with chemotherapy: in fact, most doctors reported to be unsatisfied about the available treatments and expressed the desire for a more effective therapy. In commenting on these preliminary results, the expert panel acknowledged that there is no consensus of opinion defining a clear and coordinated plan for treatment of advanced colorectal cancer and that the development of international management guidelines for optimal treatment of these patients would be desirable.

The purpose of this paper is to review the main facts which can justify a negative attitude to the treatment of advanced colorectal cancer and to make some recommendations in order to overcome the present difficulties.

IS A STANDARD CHEMOTHERAPY AVAILABLE?

Although most authors believe that the benchmark chemotherapy regimen remains single-agent 5-FU or the same drug modulated by different agents (chiefly FA) and that no combination of cytotoxic drugs is able to improve the outcome [8]; a "true" standard regimen (i.e. a well-defined treatment with a documented and reproducible survival advantage in comparison to a reference treatment or to no treatment at all, thus causing a real impact on the natural history of the disease) is not yet available.

In the last few years, many efforts have been made in order to draw some conclusions, with a potential usefulness for clinical practice, from the large number of published stu-

dies. Generally, these phase II or III studies have evaluated 5-FU associated with biochemical modulators (agents capable of increasing the activity and/or reducing the toxicity of 5-FU through an interaction with the metabolic pathways of the drug) such as FA, alpha-interferon, methotrexate (MTX) or other compounds. A major problem is represented by the great differences (in terms of dosage, dose intensity, duration of infusion, interval between the administration of the single agents, etc.) seen in studies in which apparently similar regimens were evaluated. The same observation can be made for other treatment modalities, such as 5-FU continuous infusion or intra-arterial chemotherapy for liver metastases.

There are two possible solutions for overcoming this problem. The former is to trust in few studies performed in high-profile institutions and to consider their results as a referral term for all the other centres: this solution is followed to a great extent in the U.S.A. and led, for instance, to the large use of 5-FU + levamisole in the adjuvant setting and of low-dose FA + 5-FU in advanced disease after the positive results obtained by the Mayo Clinic and collaborating centres (NCCTG) [10, 11].

The second solution is to combine all trials pertaining to a particular issue in a meta-analysis: this method (more accepted in Europe) has several advantages and some limitations [12, 13] but, with appropriate use and methodology, overcomes the lack of homogeneity of single trials in which discordant results could be reported. Of course, the basis of a good meta-analysis is represented by good-quality, well-conducted clinical trials. In advanced colorectal cancer there are interesting examples of meta-analyses aimed at particular aspects of chemotherapy.

- The value of the combination FA + 5-FU in comparison with the conventional 5-FU along was explored combining all 10 phase III trials (with the only exception being the NCCTG trial, the authors of which declined to participate) in which these two treatments were compared [14]. On a total number of 1381 patients, a significant advantage of FA + 5-FU versus 5-FU alone in terms of response rate (odds ratio = 0.44) was observed, with a slight superiority of weekly regimens in comparison with the monthly regimens (odds ratio = 0.31 and 0.58, respectively), while no difference was detected for the overall survival.
- The combination of MTX + 5-FU versus 5-FU alone was investigated combining nine phase III trials (1390 patients): a superiority for the association was documented in terms of response rate (19% versus 10%) and also of overall survival [15].
- Intra-arterial locoregional chemotherapy for the treatment of liver metastases in comparison with intravenous or *ad libitum* treatment was the subject of a recent meta-analysis on 654 patients in which a statistically significant survival advantage in favour of locoregional treatment was observed when all trials were taken into account ($P = 0.0009$). When the analysis was restricted to trials comparing intra-arterial with systemic treatment, there was still a trend in favour of the former therapy, but the difference was not statistically significant. Tumour response was 41% for patients allocated to locoregional and 14% for those receiving intravenous chemotherapy ($P < 10^{-10}$) [16].
- The value of continuous infusion versus bolus 5-FU is being studied in an ongoing meta-analysis of the same group (MAGIC: Meta-Analysis Group In Cancer) which performed the above reported studies. Another topic of interest could be the comparison of regimens employing high-dose versus low-dose FA in the biochemical modulation of 5-FU: more than 2200 patients have been entered into randomised clinical trials evaluating this question and, as the results of single studies are often conflicting, a meta-analysis seems to be warranted.

Although these trials and meta-analyses have certainly increased the knowledge about the results and role of chemotherapy in advanced colorectal cancer, the effort of defining a true "standard" treatment has failed, at least until now. Indeed, U.S.A. authorities have not tried to endorse a specific regimen in advanced disease and wide discussion is ongoing in Europe about the best treatment to use in a future adjuvant study. Therefore, the lack of a standard chemotherapy regimen could explain, to some extent, why many doctors are not convinced about the opportunity of treating patients with advanced colorectal cancer.

WHAT IS THE ROLE OF OBJECTIVE RESPONSE IN ADVANCED COLORECTAL CANCER?

In one of his last papers in 1994, Charles G. Moertel stated that "the efficacy of chemotherapy for colorectal cancer has often been judged by the so-called objective regression, usually defined as a 50% reduction in the tumour mass. This approach can be challenged for several reasons. Measurements in intra-abdominal disease are hardly precise, even with the latest imaging tools. In addition, there is no necessary correlation between the rate of objective regression and improvement in survival or quality of life for patients undergoing chemotherapy. Finally, in order to measure the extent of disease, the tumour mass must be relatively large, yet there may be important drug effects that are evident only in patients with minimal, non-measurable disease" [17]. This opinion is shared by several other authors: Middleton and Cunningham, for example, stated that "response rates should not be taken as surrogate markers for the palliative benefits of chemotherapy: symptom control and quality of life measures are far more relevant" [8]. Thus, the role of the objective response in advanced colorectal cancer is now considered less important than judged before, even though other opinion leaders do not agree [18]. Moreover, the discussion of the value of response as a surrogate marker of efficacy of a given chemotherapy is still open among the researchers who contributed to the meta-analyses reported above. An important support to the re-evaluation of the role of objective response as a measure of efficacy of chemotherapy has very recently come from the publication of ASCO Guidelines on the outcomes of cancer treatment [19]. A working group reached a consensus about the opinion that complete or partial responses are to be regarded as "cancer" (and not "patient") outcomes and that their value depends on their ability to predict patient outcomes as survival and quality of life or to influence decisions about treatment (for example, the assessment of progression is important because it signals the need to change or stop treatment).

Our opinion is that it would be better not to be too dogmatic: the achievement of an objective response remains the first and less subjective tool to assess the activity of a given treatment in a single patient and to help doctors in decision making. Unfortunately, the response rate to chemotherapy in advanced colorectal cancer is still too low to convince every clinician to treat every patient. Moreover, although the activity of various chemotherapy regimens used in the treatment of advanced colorectal cancer is assessed by different groups of investigators and in various trials by what appear to be common criteria, there may be substantial intertrial variations in the interpretation and application of these criteria which may contribute to the differing response rates reported for the same regimen. Factors such as patient selection (in terms of age, performance, status, presence of measurable disease, distribution of metastatic sites, size of liver metastases, alteration of biochemical parameters, etc.), definition and application or response criteria, assessment of time to progression or duration of response, an independent view of response, dose intensity and specific modality of administration, statistical considerations, etc. can all influence the results obtained in different trials and make intertrial comparisons difficult or even impossible. Usually a lower activity is observed when a regimen is studied outside the institution which conducted the original evaluation and when the number of treated patients has increased. This "fall effect" has a detrimental effect on the reliability of promising results and can produce a pessimistic attitude amongst the oncology community.

IS AN IMPROVEMENT OF SURVIVAL REALISTIC IN ADVANCED COLORECTAL CANCER?

The ASCO Guidelines [19] reinforced the obvious concept that survival is the most important outcome of cancer treatment. This outcome can be expressed in several ways (percentage of patients surviving at a given time—and this is perhaps the best way of representation—per cent reduction in the odds of death and median survival). In advanced disease, including colorectal cancer, it may be useful to represent survival benefit in more than one way, thus assessing thoroughly the value of a particular treatment. In the last few years, it has become more and more important to use the "quality-adjusted survival", in which the absolute length of survival is adjusted to reflect the patients' quality of life. What is the effect of the currently available chemotherapies on survival of patients affected with advanced colorectal cancer? We reported before that the few available studies in which an active treatment was compared with best supportive care alone all reported a significant increase in survival when patients received chemotherapy. However, the phase III studies comparing two different regimens are not usually able to detect a significant difference between them in terms of median survival, which often does not exceed a "plateau" of 11–12 months. The only studies in which this level is overcome are those including a large percentage of patients without measurable disease and therefore with a better prognosis [20]. This means that the lack of further survival improvement, even with new drugs or modalities of administration, can partially explain the choice of not treating patients, even though this choice is not supported by the few studies comparing chemotherapy with best supportive care alone. Of course, a significant step ahead could come if regimens showing a possible increase in survival in phase II studies should confirm this benefit in phase III trials against the best reference treatment [21].

CAN TOXICITY PREVENT A WIDE USE OF CHEMOTHERAPY IN THIS DISEASE?

Although chemotherapy in advanced colorectal cancer is usually regarded as manageable (the problem of emesis, for instance, is limited in incidence and severity), some side-effects can be serious and can induce many clinicians not to treat patients due to the risk of toxicity or to interrupt the treatment prematurely. Among these side-effects the most important are mucositis and diarrhoea for FA + 5-FU (with risk related both to the specific regimen employed and the characteristics of patients), diarrhoea and myelosuppression for interferon + 5-FU; neurotoxicity for oxaliplatin; hand–foot syndrome for continuous 5-FU infusion; and a particularly dangerous kind of delayed diarrhoea for CPT-11. Although specific supportive measures are now available against these effects (loperamide and octreotide for diarrhoea, pyridoxine against hand–foot syndrome, etc.), the fear of heavy toxicity in particular patients (elderly) or circumstances (summer season) could be another reason for avoiding a potentially active treatment.

WHICH ADVANTAGE ON SYMPTOMS CAN BE EXPECTED?

The improvement of symptoms related to cancer progression is certainly of great value for patients: the ASCO Guidelines consider this outcome to be of primary importance, chiefly if quality of life measurements are employed. These evaluations include the assessment of global quality of life, as well as its physical, psychological and social dimensions: the measures should be sensitive to clinically relevant changes induced by treatment and should avoid placebo effects and determinants not related to neoplastic disease and its therapy. The most useful setting in which to evaluate quality of life is represented by phase III studies, while the use in phase I or II trials and the introduction in clinical practice seem more problematic. The most recently started randomised studies usually include a formal evaluation of quality of life, even though a complete standardisation of the measurement instruments is not yet available. Another, and easier to apply, method of expressing the symptomatic effect of chemotherapy is the evaluation of the behaviour or a few "signal" disease manifestations, such as pain or weight decrease. The first studies that evaluated strictly the symptomatic effect of treatment showed that the percentage of patients benefiting from chemotherapy can be higher than those achieving an objective response: this means that a stabilisation of disease can be of value when coupled with decreasing symptoms. Recently, the concept of "clinical benefit" became very popular in gastrointestinal cancer after the approval by the FDA of gemcitabine in pancreatic cancer on the basis of the documentation of a subjective advantage [22]. One problem, in our opinion, could be represented by the difficult standardisation of the

evaluation criteria, both in clinical research and in everyday practice. Moreover, the emphasis on symptomatic effect of chemotherapy raises the question of whether patients without disease-related symptoms should be treated or not: as the percentage of these patients in advanced colorectal cancer is certainly high, this could be another reason in favour of a wait-and-see policy in clinical practice.

IS CHEMOTHERAPY COST-EFFECTIVE?

Only a few studies have addressed the question of whether chemotherapy is cost-effective in advanced gastrointestinal cancer: one of the most interesting papers was by Glimelius and associates [23]: the authors randomised 61 patients affected with advanced gastrointestinal cancer (21 of them with colorectal carcinoma) to either primary chemotherapy in addition to best supportive care or to best supportive care alone. The use of chemotherapy in the latter group was permitted if symptomatic treatment was not able to reach a significant palliation. The economic costs for medical care were recorded prospectively, and a cost-effectiveness analysis was performed. In the chemotherapy group, there was a significant improvement in quality of life and in survival (overall and quality-adjusted). The incremental costs were lower for gastric and colorectal cancer and much higher for pancreatic–biliary carcinoma. The authors concluded that palliative chemotherapy is cost-effective in advanced gastric and colorectal cancer, but not in patients with other primaries.

Even though the results of this study are promising, larger trials are required to achieve more accurate estimations of the palliative effects of chemotherapy. In the absence of definitive results, the scepticism of many clinicians to treat patients with advanced colorectal cancer in clinical practice can find some justification.

SELECTION OF PATIENTS TO TREAT

When clinical trials are considered, a strict selection of patients is usually performed: the inclusion criteria require patients in good general condition, without serious associated diseases, with a long life expectancy, usually not elderly (age less than 70–75 years) and often without having received previous chemotherapy. However, the availability of new promising drugs, such as Tomudex [24] and CPT11 [25], with a favourable therapeutic ratio and a well-defined activity even in pretreated patients (as in the case of CPT11), and a better understanding of cancer biology, for instance in elderly patients, could increase the field of application of chemotherapy in clinical practice. However, a wide agreement about the indications and role of cytostatic treatment in advanced colorectal cancer could be achieved, in our opinion, only through very large-scale studies in which all the discussed outcome measurements are taken into consideration. Currently, with the lack of a standard treatment and with the uncertainty of the available evaluation criteria, we feel that all potentially eligible patients should be recruited in clinical trials, whereas the others should be treated with supportive care alone or, alternatively, with the best cost-effective treatment if available. A wide use of chemotherapy outside clinical trials and without a strict evaluation of activity, efficacy and tolerability should be discouraged.

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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