Abstract. Colorectal cancer is one of the most common neoplasms in Western Countries and ranks second as a cause of death due to cancer. The overall mortality at 5 years is about 40%. Patients with resectable metastatic disease can be cured, but for those who cannot, treatment is purely palliative, and overall survival (OS) is from approximately 7 to 24 months. Infusional regimen with modulated 5Fluorouracil (5FU) gives an objective response rate (RR) of up to 30-40%. The addition of CPT11 or oxaliplatin to 5FU improves RR, time to progression (TTP) and OS with a stabilization of disease (SD) in 40-70% of cases and 20-40%, respectively. The concurrent utilization of selective biological agents as growth factor receptors acting at a molecular level and influencing the processes of tumor formation and growth, increases tumor cell apoptosis and inhibits tumor growth; as a result, the tumor regresses or is inhibited, with consequently prolonged OS and TTP. This paper examines the problem related to the treatment of metastatic colorectal cancer with SD. Current doubts regarding the continuation of one treatment until disease progression (PD) with a risk of toxicity, whether or not to use a less toxic "maintenance" therapy after a fairly aggressive "induction" therapy in "stabilized" responders, or whether to stop the treatment in the presence of a SD confirmed after at least two consecutive evaluations, are present.

Liver and lung metastases are the major cause of morbidity and mortality in patients with gastrointestinal carcinomas (1). A curative resection of these metastases is possible in 10-20% of the patients. When radical surgery resection is not possible, chemotherapy has to be considered as purely palliative (2). With the introduction of new drugs, overall survival (OS) and toxicity have improved, and the duration of treatment has become longer. A recent question is how far can a therapy be continued if there is only a stabilization of disease (SD) in "non responders" or if there is a SD (therefore, a response stabilization) in initial "responders" (with partial remission - PR - or complete remission - CR) and how important is SD for these patients. In this last case, the definition of SD means "no new tumors appear and only little change in the size of the known tumors", but it does not mean "no change". For this reason, a small amount of growth over baseline is still considered to be SD. This is appropriate since there is some uncertainty in all measurements, but it also means that over a short period of time, continued growth can still be called SD even if the treatment is not effective.

How is stable disease determined? "Genetic" and "immunological" systems as well as the "microenvironment" of the tumor and host can, "spontaneously" or "induced by pharmacological agents", determine SD. Slow growing cancers, for a natural distribution of disease growth rate, can easily appear to be relatively stable over short periods or have natural periods of relative stability; so it is often unclear if SD is "tumor-" or "treatment-related".

Genetic causes. Those factors which can cause "genetic" variability in response to treatment act during the cascade of events resulting in colorectal cancer (3-7). These events involve a series of mutations, each of which confers a proliferative advantage on cells, culminating in clonal expansion (8-10). Mutations leading to loss of function in these genes (mismatch repair - MMR - genes) lead to general genetic instability, one of the characteristics peculiar
to cancer cells (7) and to drug resistance (with consequent response to the treatment and initial SD) (11, 12).

**Immunological causes.** At the beginning of the disease, the cytotoxic reaction (T cytotoxic lymphocytes, TCL) against tumoral cells or intratumoral mutations (loss of antigen recognized by TCL) control the neoplastic mass increase thereby stabilizing its growth, but when the number of neoplastic cells increases, this control is lost and the tumor grows (Figures 1 and 2). Actually, the dynamical basis of tumoral growth is controversial. Many models have been proposed to explain cancer development and immunologic system intervention. The descriptions employ exponential, potential, logistic or Gompertzian growth laws (13) (Figures 1 and 2). Some of these models are concerned with the interaction between cancer and the immunological system. Among other properties, these models are concerned with the microscopic behavior of tumors and the emergence of cancer. Gompertzian law correctly describes solid tumor growth. The model predicts that near zero, tumors always tend to grow, but the growth fraction is not constant, therefore it decreases exponentially with time (the growth fraction peaks when the tumor is approximately 37% of its maximum size). When a patient with advanced disease is treated, the tumor mass is larger, its growth fraction is low, and the fraction of cells killed is, therefore, small. At that point, immunological contraposition never suffices to induce a complete regression of the tumor. Instead, a stable microscopic equilibrium between cancer and immunological activity can be attained, so the theory of immune surveillance is plausible. Since immunity cannot induce a complete tumor regression, therapy is required, but final levels of immunocompetent cells and tumoral cells are finite, thus post-treatment regrowth of the tumor is certain (13, 14). The response to therapy in drug-sensitive tumors depends, to a large extent, on where the tumor is in its particular growth curve.

**Microenvironment causes.** Dividing endothelial cells are present in the growing blood vessels that are found in tumors and, like other normal dividing cells, seem to be susceptible to chemotherapeutics (15) (Figure 3). Elimination of these dividing endothelial cells, or of their division, would probably lead to an anti-angiogenic effect. Moreover, as host vascular endothelial cells are assumed to be genetically stable and lack the diverse genetic defect characteristics of cancer cells that lead to drug resistance, the putative effects of chemotherapy might be more durable in the face of continued therapy. Many tumors, however, are intrinsically drug-resistant or rapidly acquire resistance after showing initial responsiveness to chemotherapy regimens. So, it would seem that chemotherapy has minimal anti-angiogenic effects. Perhaps the proportion of dividing endothelial cells in tumor-associated blood vessels is simply too low for chemotherapy to have a significant therapeutic impact. Alternatively, the endothelial cells might be protected from chemotherapy-induced cell death by high local concentration of endothelial cells survival factors, such as vascular endothelial growth factor (VEGF) or various others. A third possible hypothesis is that the anti-angiogenic effect of chemotherapy is masked by the way chemotherapy is usually administered (the long breaks between drug administration that are necessary to allow the patient to recover from the side-effects of the MTD chemotherapy reduce the anti-angiogenic effects of the drugs) (16). A state of acquired drug-resistance (with consequent "tumor-related" SD or progression of disease [PD]) could apparently be reversed by shifting the focus of the treatment away from the drug-resistant cancer cell population to the drug-sensitive tumor endothelium (i.e., with anti-VEGF) (16).

The rule of targeted therapy towards the "microenvironment" in the stabilization of colorectal cancer. A possible way to increase therapeutic activity, reduce the level of toxicity and generally to revert drug-resistance and stabilize cancer disease could be to change the pharmacological agents’ target from the tumoral cells to the tumor’s proliferating microvasculature (with more genetically stable cells),
Figure 2. When a CR or PR are achieved, the growth fraction decreases exponentially with time but after a brief period, it tends to grow again.

When a SD is achieved, the growth fraction temporarily terminates but after a longer period than after CR or PR, it tends to grow again.
modifying (with no prolonged drug-free breaks) their high dose to a continuous and/or daily, lower dose (a tenth to a third of the MTD) with the so called "metronomic" administration (17). The anti-angiogenic properties of this form of administration (with consequent apoptosis of endothelial cells in the vascular bed of tumors and with minimization of total tumor burden, rather than complete eradication) could also be further increased by the concurrent utilization of selective angiogenesis inhibitors acting at a molecular level and influencing the processes of tumor formation and growth. Such inhibitors increase tumor cell apoptosis and inhibit tumor growth by inhibiting endothelial proliferation and migration and/or by inducing endothelial apoptosis (18, 19). As a result, endothelial apoptosis would precede tumor cell apoptosis, and therefore the tumor regresses or is inhibited (with consequent SD), whether or not the tumor cells are resistant to the drug, and with little or no host toxicity. The absence or reduction of intratumoral vascularization should reduce tumor nutrients and oxygenation, blocking disease proliferation but not causing extensive tumor regression (20).

Bevacizumab (Avastin), the new drug introduced for the treatment of metastatic disease, favorably neutralizes VEGF, one of the best characterized pro-angiogenic growth factors, by blocking its ability to activate its receptor on the endothelial cells (21). In colorectal cancer, an increased
expression of VEGF correlates with invasiveness, vascular density, metastases, recurrence and prognosis. In patients with significant tumor burdens, anti-VEGF, a recombinant humanized monoclonal antibody to VEGF, decreases tumor blood perfusion and volume, interstitial fluid pressure, the number of circulating endothelial cells and fluorodeoxyglucose uptake, thereby prolonging TTP and OS and stabilizing disease more than inducing tumor regression (7). It is still unknown whether targeting one factor or a limited profile of factors provides meaningful antitumor activity for most patients or for only an undefined subset. In the advanced disease, tumors have already activated various pathways that allow them to easily override the angiogenic restriction of one inhibitor (22). A more successful approach could involve combinatorial strategies to target cells themselves (i.e. anti-VEGF plus anti-epidermal growth factor receptor EGFR), along with the stroma (that is made up of endothelial, perivascular and inflammatory cells) or with conventional therapy (cytotoxic agents acting in a synergic way but with a different mechanism). In combination with 5FU-based chemotherapy, which amplifies the pro-apoptotic effects of the chemotherapeutics against activated endothelial cells, but presumably not against other types of normal dividing cells (23), the anti-VEGF bevacizumab, improves TTP (9.0 versus 5.2 months) and OS (21.5 versus 13.8 months) (24). The addition of CPT11/5FU/leucovorin (LV) (IFL) is associated with an increased median duration of progression free survival (PFS) (10.6 months versus 6.2 months in comparison with the group given IFL plus placebo; \( p<0.001 \)) and response (10.4 months versus 7.1 months, \( p=0.001 \)) (25).

The duration of therapy required for an effective treatment remains an unanswered question. Because of the anti-angiogenic stabilization action, long-term (and possibly low-dose metronomic) chemotherapy could be necessary, whether or not it leads to tumor resistance or late toxicities. Whereas some preclinical studies in mice report exceptionally long-term tumor response (and stabilizations), and in some cases mice were even cured (16, 23), most mice eventually relapsed (26, 27). This indicates that some forms of acquired resistance occur – either at the host-level (such as through altered metabolism), the tumor-cell level (such as through selection for mutant tumor cells that can survive under the hypoxic condition created by inhibition of angiogenesis) (26) or at the level of endothelial-cells or blood vessels, such as vascular remodeling into more mature vessels that are less responsive to anti-angiogenic treatment (27).

EGFR over-expression, one of the tumoral and host microenvironment key signaling networks, provides the rationale for another type of targeting therapy. An EGFR blockade through monoclonal antibodies (C225 or Cetuximab) and tyrosine kinase inhibitors (ZD1839, gefitinib or Iressa and OSI-774, erlotinib or Tarceva) is associated with an improved "clinical benefit" (CB) (24). Cetuximab (Erbitux), a chimical monoclonal antibody highly selective for the EGFR over-expressed by 25-80% of colorectal cancer tumors with advanced disease, induces a broad range of cellular responses in most, but not all, tumors expressing EGFR (apoptosis promotion, cell proliferation, angiogenesis and metastases inhibition). It also enhances sensitivity to radio-chemotherapy to which cancer cells have become resistant. In colon carcinoma, an autocrine loop exists whereby ligands for the EGFR activate the receptor. By inhibiting the autocrine or paracrine activation of the EGFR, tumor cells that may typically survive in their caustic microenvironment with low pH and \( \text{pO}_2 \) tension, may undergo spontaneous apoptosis. In this case, this so-called "cytostatic"-targeted therapy may acquire a therapeutic potential, leading, not only to tumor stabilization, but also to tumor cell apoptosis and regression because of the inhibition of critical signaling pathways (28). While the vast majority of preclinical data with cetuximab alone has primarily demonstrated cytostatic activity and modest efficacy, data combining cetuximab with marginally effective or ineffective cytotoxic chemotherapy have demonstrated marked synergy with dramatic improvement in antitumor activity (29). Increased disease control (CR + PR + SD: 33.8% versus 56.3%, \( p=0.0032 \)) and longer times to disease progression (1.5 versus 4 months, \( p<0.001 \)) have been obtained with cetuximab in combination with CPT11 in irinotecan-refractory patients (30, 31), circumventing irinotecan-resistance by abrogating drug efflux (32), restoring apoptosis (33), and impairing DNA-repair activity (34). The one-year survival rates of 29% in the combination-therapy group and 32% in the monotherapy group were encouraging.

In a phase II study on chemo naive patients, the same combination produced 50% PR, 5% CR and 42% SD (35), but more trials and longer follow-up are needed to confirm these results and their importance in terms of SD.

Stable disease in colorectal cancer. The role of cytotoxic drugs. For the last 4 decades, synthesis and testing of potentially active drugs (i.e., antimetabolites) have focused on structural modification of existing metabolites as precursors of DNA and RNA synthesis. In recent years, the focus of the research on new biological strategies for the treatment of metastatic colorectal cancer has shifted to the synthesis of target-specific agents such as TS (36). TS is a critical target for 5FU and its prodrugs, UFT/LV (Orzel), capetabine (Xeloda) and S-1, primarily because this enzyme is essential for the synthesis of 2-deoxythymidine-5-monophosphate, a precursor for DNA synthesis. While fluoropyrimidine antimetabolites have other sites of action, antifolates ZD1694 (ralitrexed or Tomudex) and AG337 (Thymitag) are more specific and potent TS inhibitors. Thus, it is hoped that pronounced and
sustained inhibition of this enzyme could result in
downstream regulation of molecular markers associated with
sensitivity and resistance to these agents. It has also been
found that thymidine phosphorylase (TP), the activating
enzyme for 5FU, and the pyrimidine catabolism enzyme
dihydropyrimidine dehydrogenase (DPD) are involved in
tumor response. Patients with low expression of all 3 of
the genes have significantly longer survival than those with a
high value of any one of the gene expressions; the
intratumoral gene expression level of DPD is associated with
tumor response to 5FU (37), while high gene expression of
TS (38) and TP (39) identifies non-responsive tumors to
5FU-based therapy. The use of more than one independent
determinant of response now permits the identification of a
high percentage of responding patients.

Most cytotoxic chemotherapies are DNA-damaging
agents or microtubule inhibitors designed to inhibit or kill
rapidly dividing cells. They are often administered in single
doses or short courses of therapy at the highest doses
possible without causing life-threatening levels of toxicity
(MTD). MTD therapy requires prolonged breaks (generally
of 2-3 weeks) between successive cycles of therapy. Despite
the number of such chemotherapies and the huge number
of clinical trials that have been undertaken to test them,
progress has been modest in terms of curing or significantly
prolonging the lives of patients with cancer. Moreover, the
progress that has been made in treating certain types of
malignancy often comes at a high price, given the toxic
effects that are frequently associated with MTD-based
chemotherapy.

In the prospective randomized trials which became the
basis for the U.S. (40) and European (41) approval of
CPT11 and Oxaliplatin (42) as first line treatment for
metastatic colorectal cancer, the duration of the objective
response was stressed (range, 9-11 months in all groups),
but the concept of TTP or SD and whether it was ongoing,
was not specified (Table I). Treatment continued until
disease progression, unacceptable adverse effects, or the
withdrawal of consent by the patient. Analyses of CB
and quality of life (QoL) showed no significant differences
between the different groups of patients (5FU/LV versus
5FU/LV/CPT11 or 5FU/LV/Oxaliplatin), so a symptom
improvement was not described or, did not appear to
influence the benefit or duration of chemotherapy.

Fages et al. (43) investigated 455 patients with 5-FU
resistant disease and found correlation between OS and
response, where RR and SD were independent prognostic
factors \( p<0.001 \), which appeared to be a reliable surrogate
endpoint for survival. Relatively low RR was compatible
with significant patient benefit if responses and
stabilizations were long-lasting.

To get a better picture of the best length of time for
treatment with anticancer drugs on patients without PD, a
randomized trial was designed (44). It is clear that patients
receiving short-course chemotherapy could have a shorter
TTP, but some investigators (45, 46) have reported that at
the time of PD, patients can be successfully rechallenged
with the same regimen. For this reason, in the first arm of
the study, 178 patients were randomized to stop the
treatment at the SD or at the response after an initial 12
weeks of chemotherapy. Sixty-six of the patients rechallenged
with the same regimen. For this reason, in the first arm of
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<table>
<thead>
<tr>
<th>Authors</th>
<th>Drugs</th>
<th>No. PTS</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
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<tbody>
<tr>
<td>Saltz</td>
<td>IFL (with 5FU/LV bolus) vs Mayo Clinic vs CPT11 125 mg/m2/wk x 4 wks q 6 wks</td>
<td>683</td>
<td>39 vs 21 vs 21 (( p&lt;0.001 ))</td>
<td>14.8 vs 12.6 vs 12.0 (( p&lt;0.04 ))</td>
</tr>
<tr>
<td>Douillard</td>
<td>AIO or &quot;FOLFIRI&quot; (with infusional 5FU/LV) vs 5FU 2600 mg/m2 vs 24 hours c.i.+ LV vs 500 mg/m2/wk or de Gramont regimen</td>
<td>387</td>
<td>49 vs 31 vs 31 (( p&lt;0.001 ))</td>
<td>17.4 vs 14.1 vs 14.1 (( p&lt;0.031 ))</td>
</tr>
<tr>
<td>de Gramont</td>
<td>'FOLFOX' 4 (with 5FU/LV infusion) vs de Gramont</td>
<td>420</td>
<td>50.7 vs 22.3 vs 22.3 (( p&lt;0.0001 ))</td>
<td>16.2 vs 14.7 vs 14.7</td>
</tr>
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</table>

q = every; wks = weeks; c.i. = continuous infusion; mo = months; vs = versus; pts = patients; RR = response rate; MST = median survival time; 5FU = 5Fluorouracil; LV = levamisol.
CPT11 and Oxaliplatin with 5FU/FA provided unprecedented response and survival benefits as first- or second-line therapy with a strong safety profile and an improved QOL; median duration of response was 8-11 months; duration of SD or TTP was not reported.
Thus, these findings provided no clear evidence of a benefit in continuing therapy indefinitely until PD. Even if "intermittent" therapy in some cases leads to earlier PD, retreatment on PD, delaying the emergence of drug-resistant clones and improving long-term cancer-control, prevents a substantial detriment to survival; moreover, improved QoL during periods without chemotherapy, compensates for earlier PD.

According to the authors, the actual problem in these patients could be related, first to the duration and effectiveness of the induction therapy to ensure the best response; a long induction therapy could lead to drug resistance, and subsequent rechallenging could be less effective. Patients should also achieve a good response to the rechallenged therapy. Furthermore, the time between termination of the induction therapy and PD should be relatively long in order to obtain a better response. Lastly, patients out of treatment should be frequently followed until PD, in order to restart therapy quickly at the first sign of progression. Although this trial was undertaken with a monochemotherapy (5FU or raltitrexed), similar results have also been recently confirmed with the introduction of new agents, such as oxaliplatin or CPT11 (47). Additional costs and toxicity related to these drugs, can be a future justification for an intermittent therapy with consequent delay of a second-line therapy until the rechallenged regimen fails.

A more recent and a slightly different approach is the so called "stop and go". A phase III randomized study on 526 patients (49) (Table II) was presented by the OPTIMOX trial. The FOLFOX 4 regimen administered continuously until PD (arm A) was compared with FOLFOX 7 regimen, followed by 12 cycles of simplified 5FU/LV and later by FOLFOX 7 reintroduction (arm B). RR was similar (58.8% in arm A and 59.5% in arm B); median PFS was 9.2 and 9.0 months ($p=0.47$), and median OS was 20.7 and 21.4 months ($p=0.75$), respectively. Due to similar results, the arm B strategy appeared to be a convenient alternative in terms of costs and toxicity to FOLFOX 4 administered until progressive disease.

A similar study conducted in 37 elderly patients (50) indicated that the use of a less toxic maintenance therapy after a fairly aggressive induction therapy resulted in equivalent TTP and OS (65 weeks in arm A and 90 weeks in arm B) when compared with a more conventional treatment given until patients could not continue or had PD. The results of this trial are intriguing but will need to be confirmed in larger randomized trials before being accepted as the new standard of care.

To further increase long-lasting SD in a pathology such as colorectal cancer, in which OS has recently improved

| Table II. Optimox trial (49). |

<table>
<thead>
<tr>
<th>Induction therapy</th>
<th>Maintenance Therapy</th>
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<tbody>
<tr>
<td>FOLFOX 4 until PD</td>
<td>FOLFOX 7 x 6 cycles</td>
</tr>
<tr>
<td>vs</td>
<td>LV5FU x 12 cycles</td>
</tr>
<tr>
<td>RR 58% vs 64% ($p=ns$)</td>
<td>OS 20.7 vs 21.4 months ($p=ns$)</td>
</tr>
<tr>
<td>PFS 9.2 vs 9 ($p=ns$)</td>
<td>TDC=post FOLFOX + PFS post FU/LV if PR or SD=9.9 vs 11.3 months ($p=ns$)</td>
</tr>
</tbody>
</table>

$\text{vs}=\text{versus}; \text{PD}=\text{progressive disease}; \text{RR}=\text{response rate}; \text{PFS}=\text{progression free survival}; \text{OS}=\text{overall survival}; \text{TDC}=\text{time of disease control}; \text{PR}=\text{partial remission}; \text{SD}=\text{stable disease}; \text{5FU}=\text{5-fluorouracil}; \text{LV}=\text{levamisole}; \text{ns}=\text{not significant.}$

The OPTIMOX "stop and go" strategy is a convenient alternative in terms of costs, toxicity, PFS and OS to FOLFOX 4 administered until progressive disease.
with the introduction of new drugs, a different way of administration of the same drugs has been studied. The effectiveness and toxicity of many agents can vary depending on the time of administration in relation to 24-hour circadian rhythms of biochemical, physiological and behavioral processes, thus giving rise to chronotherapy (51).

Such chronopharmacological phenomena are influenced, not only by the pharmacokinetics of medications, but also by their pharmacodynamics.

The 24-hour rhythm of DNA synthesis and the activity of DPD brings about the intracellular catabolism of 5FU. On the other hand, haloperidol and selective serotonin reuptake inhibitors have diverse effects on sleep continuity and nocturnal awakenings.

Although interferon also alters the internal clock function, this disruptive effect can be overcome by devising an administration regimen that minimizes adverse drug effects on the internal clock. Thus, one approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated.

Disruption of these circadian rhythms in mice is associated with accelerated growth of malignant tumors, suggesting that the host circadian clock may play an important role in endogenous control of tumor progression. To confirm these results, a phase II clinical trial with 5FU/LV combined with oxaliplatin involving 93 patients was carried out (52). Fifty-four of the 93 patients had an objective response (58%). CR were seen in 6 patients and, after surgery, in 12 additional patients (19% CR). Median PFS and OS were, respectively, 10 and 15 months, significantly longer in patients with a good PS (12 and 21 months, respectively) than in those with poor PS (8 and 10 months, respectively, \( p<0.01 \), as confirmed subsequently by Popov et al.) (53).

To attest these results, Levi et al. (54) administered the same drugs with a chronomodulated infusion and compared them with a constant-rate infusion method.

Chronotherapy was significantly less toxic and more effective than constant-rate infusion. An objective indicator of physical welfare and QoL also emerged. The median time to treatment failure was respectively 6.4 and 4.9 months \( (p=0.006) \). With a minimum follow-up of 3 years, MST and 3-year OS were similar in both groups (15.9 \textit{versus} 16.9 months and 22% \textit{versus} 21%, respectively) (55-58).

A recent European multicenter trial (59) validated the clinical relevance of the same concept in 200 patients from 15 institutions in 4 countries. They were randomly assigned to receive a 5-day course of chronomodulated 5FU/LV, with or without oxaliplatin, on the first-day of each course. Sixteen percent of the patients receiving 5FU/LV had an objective response (range, 9% to 24%), compared with 53% of those receiving additional oxaliplatin (range, 42% to 63%) \( (p<0.001) \). The median PFS was 6.1 months with 5FU/LV (range, 4.1 to 7.4 months) and 8.7 months (range, 7.4 to 9.2 months) with oxaliplatin and 5FU/LV \( (p=0.048) \). MST were 19.9 and 19.4 months, respectively. Oxaliplatin significantly improved the antitumor efficacy of this regimen in terms of SD, CB and long resting responses (51).

**What does Stable Disease really mean?**

SD in "non-responders". An increasing number of papers

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**Table III. The Popov et al. study (53).**

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<tr>
<th>Condition</th>
<th>Probability</th>
<th>Significance</th>
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<tr>
<td>OS similar to CR + PR (( p=0.24, \text{ns} ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS different from PD (( p=0.000005 ))</td>
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PD=progressive disease; OS=overall survival; PR=partial remission; SD=stable disease; CR=complete remission; ns=not significant

Patients with SD and CB could be a target group for policy "to treat until PD"; patients with SD but without symptom improvement have no benefit from further chemotherapy and in these patients treatment should be stopped sparing them from unnecessary toxicity.
treat SD as evidence that the therapy in question benefits or holds promise for the treatment of advanced cancer. Some authors combine the concepts of SD and objective response, defining them as CB, and some press releases play up CB, as evidence that the treatment is promising, even when the majority of cases of alleged benefit are SD.

In the Popov study (53) (Table III) on 97 evaluable patients whether SD with CB was associated with a benefit.
in survival or TTP was investigated, and no difference was detected between responders and "SD-CB" patients ($p=0.24$), but there was a significant difference between responders and patients with SD without CB ($p=0.0004$). SD-CB patients also displayed significant difference compared to those with PD ($p=5.1x\times10^{-6}$).

The results of this study indicate that under the category "SD" there are two different subpopulations of patients with quite different symptom responses and improvements in QoL as an effect of chemotherapy, different TTP and perhaps even different survivals ($60$).

"Symptomatic patients" at diagnosis, with subsequent SD, but who never achieve PR or CR, and CB, could be a target group for the "treat until disease progression" policy. Patients with SD, who have not achieved PR or CR, but without symptom improvement, have no benefit from further chemotherapy, so the treatment should be stopped to spare patients unnecessary toxicity. In reality, we have no data as to whether a different number of chemotherapy cycles in the groups of patients with and without CB could lead to a bias in survival estimation. "Asymptomatic patients" at diagnosis, with SD, who are still asymptomatic after 4 chemotherapy courses, make up a group for which it is hard to make a decision to either continue or stop chemotherapy.

SD in "responders". A current problem is understanding the duration of the responses of disease, or rather the "time of SD" which elapses from the best response, PR or CR, to PD, in "responders". Preliminary reports of SD are usually based on short follow-up (only 8-12 weeks) and only sometimes mention if and how SD is still ongoing.

Conclusion

In metastatic colorectal cancer the infusional regimen with 5FU gives an objective RR of up to 30% to 40%, but the addition of CPT11 or oxaliplatin to the same drug improves not only RR, but also TTP, response duration and OS ($61$-$64$). The introduction of these new agents and of biological agents has further increased TTP from 3 to 10 months and OS from 7 to 24 months. These prolonged responses (time between the maximal response and PD, according to the RECIST criteria) or disease stabilization (time between the beginning of the treatment and PD or TTP) have created the doubt regarding how long to continue a treatment in tumor-responders. According to WHO criteria, a tumor with "SD" has been defined as a "disease responding less than 50% and not increasing more than 25%", but a PD less than 25% has to be considered as a PD more than a SD. The concept changes according to different kinds of tumors or metastases (i.e., in the presence of bone metastases, a SD for more than 4 months could be defined as PR) but it is important for those tumors growing slowly or for those commonly aggressive or chemoresistant ($65$) for which CB is more important than the achievement of a RR. A good compromise could be obtained by distinguishing between "responders" or "non responders" achieving a SD those that are "symptomatic" at diagnosis from those which are "asymptomatic". Patients would then be evaluated for clinical improvement, and those with CB would be treated until PD with the same therapy or with metronomic or chronomodulated infusion, or by alternating an induction therapy with a continuative therapy to prolong the responses, thereby reducing the toxicity rate (Tables IV and V).

Currently, there is little clinical data supporting SD as an endpoint or the utility of continuing treatment until PD, and useful guidelines are lacking. Common clinical practice varies little from the clinical trial attitude. Sometimes, therapy is stopped after two subsequently instrumental checks for SD and is re-initiated after a new PD, with either the original therapy (in the case of relapse of at least 3 months after the discontinuation of 4-6 months of successful treatment) ($44$, $66$), or with another therapy. However, the characteristics of this approach are still unclear. The recent introduction of biological therapy, which has a better effect on biological tumor cell cycles since the response duration rather than the response is influenced, may help to resolve these problems. New drugs, such as bevacizumab or cetuximab which have greater cytostatic than cytotoxic effects could therefore be useful in prolonging the positive results already obtained with the cytotoxic chemotherapeutic agents oxaliplatin and CPT11.

References


