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Adjuvant chemotherapy in colon cancer

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Out of the million of patients (pts) worldwide who will have a colon cancer in 2010, approximately 50% will have a stage II or III colon cancer (CC) and for most of them the question of administration of an adjuvant treatment will be raised.

According to the 6th AJC classification stage II is subdivised into IIa (T3, N0) of excellent prognosis and IIb (T4, N0) of worst prognosis; stage III has been divided into IIIa (T1 or 2, N1) of excellent prognosis, IIIb and IIIc of worst prognosis. The aim of adjuvant chemotherapy is to decrease the risk of recurrence and to increase the overall survival (OS).

For stage III CC the efficacy of adjuvant chemotherapy is established with a large consensus in favour of the administration of adjuvant chemotherapy since 1989 when 5FU-levamisole for one year demonstrated its efficacy. In 1996 it was demonstrated that 5FU + leucovorin for 6 months had a better therapeutic index and in 2003 that continuous 5FU for 3 months was also efficient. Later on, oral 5FU demonstrated its interest in the X-ACT protocol which reported that 6 months of oral capecitabine was as efficient (and even a little better) than 5FU-Leucovorin as well as oral UFT in the NSAPB C06. In 2004, a major step was done with the demonstration that the FOLFOX 4 regimen was better than 5FU-Leucovorin *(Andre T et al. N Engl J Med 2004)* with an increased DFS (HR of 0.77), and in an update analysis an increased overall survival (HR: 0.84; p=0.046) *(JCO 2009;27:3109)*. In the US, beside the FOLFOX4 regimen mainly used in Europe, the combinations of bolus 5FU/FA and oxaliplatin (FLOX) also demonstrated its efficacy in the C-07 trial with an improved DFS for stage II and III CC with a relative decrease of 20% in the recurrence rate (HR: 0.80; p<0.004) *(Kuebler JP et al, JCO 2007;25:2156)*. Recently the XELOX protocol which combines oral capecitabine (14d on, 7 days off) and an every 3 weeks administration of oxaliplatine demonstrated the same efficacy compared to 5FU-Leucovorin (3-years DFS HR: 0.80; p=0.0045) *(Haller DG et al. ASCO 2010; JCO 2010 ;28:266s)*.

The benefit of oxaliplatin containing regimens over 5FU-Leucovorin in patients over 70 years of age were discussed because there was no clear evidence of efficacy in a meta-analysis *(McCleary ASCO 2009)*. However, in 2 trials there was a benefit in DFS with the use of FOLFOX *(Tournigand ASCO 2010)* and XELOX regimens *(Haller D et al. ASCO 2010)* without benefit in OS. In fact, the absence of benefit in OS when the 5-year survival was looked at, may be related to the need to have a longer follow-up to observe a difference as de Gramont reported that a follow-up of 6 and 7 years was necessary rather than 5-year follow-up to find a correlation between DFS and OS when FOLFOX regimen is used.

For stage II colon cancer there is no consensus concerning their management. The main reason for such incertitude is due to the fact that there is no large positive trial conducted in this specific population and because a low risk of relapse (15% to 30%) as well as a low risk of death (10% to 20%) and a potential absolute gain in overall survival (OS) estimated, for an HR of 0.80 in favour of chemotherapy, which ranges between 2% and 5%.

However, 5 meta-analyses and two trials, the QUASAR 2 and the MOSAIC gave us some indirect arguments in favour of the efficacy of adjuvant chemotherapy using a 5FU based regimen for stage II colon cancer pts. The two meta-analyses were borderline positive: the IMPACT B2 was a pooled analysis of 5 randomized trials (1016 pts) which reported an advantage of 2% (82% vs 80%) in favour of a 5FU and folinic acid combination but this difference was not significant (HR=0.86, p=0.057) *(IMPACT B2, J Clin Oncol 1999;17:1356-63)*; the Canadian meta-analysis conducted on 8 trials comparing surgery alone to surgery plus a 5FU based chemotherapy (1870 pts) also reported the same HR of 0.86 but also was not significant (p=0.057) *(Figueredo et al. J Clin Oncol 2004;22:3495-3507)*. Two meta-analyses were positive but the NSABP meta-analysis was a compilation of heterogeneous trials *(Mamounas E et al. J Clin Oncol 1990;17:1349-55)*, and, the Japanese meta-analysis on 5233 pts was conducted in an heterogeneous group of pts with only 45% of stage II colon cancer for whom a + 4.3% increase in OS in favour of an oral 5FU based chemotherapy was reported *(Sakamoto J et al. J Clin Oncol 2004;22:484-92)*. The last was a meta-analysis from the Mayo Clinic which was positive for the DFS (76% vs 72%; p=0.049) but not for OS (81% vs 80%, NS) *(Gill et al. J Clin Oncol 2004;22:1797-806)*.

The QUASAR 2 study is the largest trial conducted in part in stage II colon cancer and compared, for pts with an uncertain benefit from chemotherapy, a group of pts treated by surgery alone (n=1617) to a group receiving a post-op 5FU and folinic acid combination (n=1622). This trial reported a significant difference in OS (5-year survival: 83% vs 80% in favour of chemotherapy) (HR: 0.82; p=0.008). However, only two thirds of the pts had a stage II colon cancer in this trial *(Gray R et al. Lancet 2007;370:2020-9)*.

In the MOSAIC trial, approximately 40% of the pts had a stage II colon cancer and these pts benefited from the same relative risk of recurrence reduction as the stage III colon cancer, however the DFS was not significantly ameliorated by the administration of the FOLFOX4 regimen compared to LV5FU2 (3-year DFS: 84.3% vs 87%; HR: 0.80 [IC95%: 0.56-1.15]) because the trial was not powered to answer questions for stage II colon cancer *(Andre T et al. N Engl J Med 2004)*. However, in an updated analysis de Gramont reported a significant increase in DFS for high risk stage II patients receiving FOLFOX (HR: 0.76; *de Gramont, ASCO 2005*).

In fact stage II colon cancer pts are a very heterogeneous group of pts which must be separated according to prognostic factors. For instance, in the large SEER cohort reported in 2004 there was an important difference in the OS of pts pT3N0 (stage IIa) (5-year OS: 83%) compared to pts with pT4N0 (stage IIb) (5-year OS: 72%) *(O'Connell et al. J Natl Cancer Inst 2004;96:1420-5)*. Since about 10 years ago, a high risk subgroup of stage II colon cancer has been defined concerning pts with perorated or obstructive or pT4 tumors *(Schrag D et al. J Clin Oncol 2002;20:3999-4005)*. In some studies other factors like the existence of vascular invasion by the tumor, a poor differentiation or a number of analysed lymph nodes < 10 were considered as poor prognostic factors *(de Gramont et al. N Engl J Med 2004;351:1691-2; Moris M et al. Br J Surg 2006;93:866-71; Sarli et al. Eur J Cancer 2005)*. Biological markers may also influence the risk of recurrence and for instance the MSS status is recognized as a factor of poor prognosis as well as the presence of a 18q LOH. For pts having one of these poor prognostic factors and without counter-indications to receive a chemotherapy there is an agreement to prescribe an adjuvant chemotherapy for stage II high-risk pts who ask for after clear informations on the benefit/risk ratio of the adjuvant chemotherapy (5FU-folinic acid combination or FOLFOX4 regimen). Thus, if there is no consensus on the standard adjuvant treatment for stage II colon cancer pts, in case of high risk of recurrences there is an agreement to propose an adjuvant chemotherapy to selected and informed patients. Ongoing trials will help to precise the role of adjuvant chemotherapy in stage II colon cancer, in particular the ECOG E5202 trial which compares, in stage II MSS or 18q LOH, a chemotherapy (FOLFOX6) to a combination of this chemotherapy with bevacizumab.

The role of targeted therapies and of new molecular prognostic or predictive factors are two important aspects which are presently under investigation for high risk CC:

- Concerning the targeted therapy, it has been reported *(N Wolmark ASCO 2009)* that the addition of bevacizumab to the FLOX regimen did not ameliorated the DFS, even if a transitory effect during the year of administration was reported. At ASCO 2010, it has been reported that the combination of cetuximab and the FOLFOX6 regimen (trial O147) does not improve the DFS and was even deleterious in KRAS mutated patients and in elderly patients *(S Alberts et al. ASCO 2010 lba CRA3507; JCO 2010;28:959s)*.
- Concerning the molecular prognostic factors it has been confirmed that patients with MSI-high tumours have a better prognosis than MSS or MSI-low tumours *(Roth A et al. ASCO 2009; JCO 27:15s)* and were not responsive to 5FU chemotherapy *(Sargent D et al. JCO 2010;28:3219)*. 18qLOH is a marker of poor prognosis in case of deletion; however this allelic loss does not seem to influence the sensitivity to adjuvant chemotherapy. At the last 2010 ASCO meeting different genes signatures have been presented and each was more or less significantly associated with the outcome of the patients, however no data supported that these signatures were predictive for adjuvant chemotherapy efficacy.

In conclusion, adjuvant chemotherapy in stage III and high risk stage II CC is efficient and improve the DFS and at a lesser extend the OS. In the future we will have to ameliorate the efficacy of the adjuvant CT and/or to decrease its toxicity, this is the aim of the IDEA trial comparing 3 vs 6 months of treatment. In all the cases it is important to discuss the cases of all patients at multidisciplinary staff meetings and to keep tumour specimens in formalin and if possible frozen for further molecular studies, which may be useful for the treatment of the patients or for genetic counselling.

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Therapy for metastatic colorectal cancer

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Colorectal cancer (CRC) is one of the most common cancers in the world. Over half of patients with colorectal cancer will develop metastatic disease, with a quarter having distant metastatic lesions at diagnosis, often in liver (1). Surgical resection of colorectal liver metastases is a potentially curative option, with reported 5-year survival of 28-39%. However, about 80% of patients with colorectal liver metastases have unresectable disease at presentation and long–term survival is low (2). In the EORTC 40983 trial for resectable liver metastases, resectability was defined as being technically resectable and four liver metastases or fewer (3). Nowadays, it is accepted that experienced surgeons can carry out all kind of operations, including multiple resections, provided that there is sufficient remnant liver (more than 30%), presence of questionably resectable extrahepatic disease and surgery is not too risky due to location (proximity to vessels of the anticipated remnant liver).

Multidisciplinary oncology team faced three clinical scenarios when assessing patients with colorectal liver metastases: a) patients with readily resectable metastatic disease, b) metastatic disease that is initially considered to be unresectable, principally due to location and c) those patients that are unlikely ever to become resectable.

Treatment practice is likely to be surgery for resectable liver disease but today chemotherapy even in the patients with resectable metastases, can increase the complete resection rate, facilitate limited hepatectomies, provide a test of chemoresponsiveness, identify aggressive disease spare ineffective therapy and prolong relapse free survival (RFS). This is supported by the results of the EORTC 40893 study where the PFS rate at 3 years was increased by 9.2% in those patients who received perioperative chemotherapy when compared with surgery alone in the actually resected group of patients (5). For patients with unresectable and unlikely to ever become resectable disease, treatment practice is palliative chemotherapy. The combination of chemotherapy and surgery is currently accepted as the way forward for improving survival in patients with initially unresectable colorectal liver metastases (5).

Standard chemotherapy regimens with 5-Fluoauracil (5-Fu) has been the exclusive treatment for metastatic CRC for more than 40 years resulting response of 15% and modulation with leucovorin (LV) increased the response rate up to 25% (6). In the last 10 years the combinations of 5-Fu/LV with oxaliplatin (FOLFOX) and irinotecan (FOLFIRI) have been shown to be superior to 5-Fu/LV in terms of both response rate (56% FOLFIRI and 54% FOLFOX) and survival, resulting for the first time in median survival of 20 months (7).

Data emerging from randomized trials suggesting that the addition of targeted agents and a third cytotoxic might be even more effective. The monoclonal antibody against vascular endothelial growth factor (VEGF) bevacizumab in combination with chemotherapy yielded median survival of 25 months (8). The results of another monoclonal antibody, which blocks epidermal growth factor receptor (EGFR) cetuximab in combination with chemotherapy, increased the response rate up to 80% with KRAS wild-type tumors. (9).

Current treatment practice for patients with initially unresectable metastatic disease is to treat with the most effective regimen (4) but the question then becomes «what defines the most active regimen in the clinical setting?» It would be perioperative chemotherapy in patients with colorectal liver metastases which would not only shrink the tumor but also reduce the recurrence rate by killing any micrometastases that might remain after surgery.

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