Medical treatment for peritoneal carcinomatosis from colorectal cancer

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Introduction

Colorectal cancers (CRC) are estimated to rank third in incidence in men in Europe and are the second most frequent cancers in women. Approximately 60.000 people will die from colorectal adenocarcinomas among the 150.000 new cases which will be diagnosed this year.

Peritoneal carcinomatosis (PC) complicates the evolution of around 10% of CRC, especially when the primary tumor was perforated or obstructive. PC are seldom isolated and most are combined with liver, ganglionary or ovarian metastases. When PC are isolated surgical excisions are feasible in some rare cases and in these cases local and systemic chemotherapies may have a role to prevent recurrences (but this is not yet clearly demonstrated), when no surgical excision is possible systemic chemotherapy may have a real palliative effect allowing in some cases long term survival. Its medical treatment can be symptomatic and/or antitumoral.

1) *The symptomatic treatment* comprises steroids in case of intestinal obstruction, pain killer avoiding if possible morphinic in case of pain, ascitis drainage in case of abdominal distension with ascitis ...
2) *The antitumoral treatment* is mainly represented by chemotherapy (CT) and may also have a symptomatic effect. The efficacy of systemic CT is the same for rectal cancer than for colon cancer and there is no proof that PC is less responsive to 5FU combination than liver metastases in contrast with lung metastases which are significantly less responsive, probably for biological reasons (high TS level or hyperexpression ?). Combination of 5FU and folinic acid increased survival arid quality of life in two randomized trials reported by Scheitauer (1) and the Nordisk Group (2). In the last study the symptom free survival in patients without symptoms at diagnosis was prolonged even if there was a proven PC.

Concerning the type of chemotherapy regimens, after 40 years, 5FU is still the main drug and we still learn a lot about it !

– *The 5 FU story* (fluorouracil, Roche lab.) : Important improvements have been made these last ten years in the use of 5FU : modulation of 5FU by folinic acid (3) and the use of continuous perfusions using high dose 5FU administered during 24 to 48 hours weekly or beweekly result in higher response rates than observed with bolus administration (20 to 30% vs 10 to 15%) (4,5). Serum 5FU determination with doses adaptations according to pharmacological studies with dose adaptation resulted in less toxicity and a better response rate. In a near future it will be possible to use oral precursors of 5FU like capecitabine (Xeloda®) which acts more selectively on the tumor cells and are very convenient for the patients if they have no absorption problems and gave higher response rates than the 5FU modulated by folinic acid (proc ASCO 1999 ; 18 : 263a # 1010 and 265a # 1016) ; UFT which combines a 5FU prodrug (ftorafur) and a DPD inhibitor (uracile) has an activity equivalent to the 5FU modulated by folinic acid (proc ASCO 1999 ; 18 263a # 1009 and 264a # 1015). In certain situations, Raltitrexed (Tomudex®) which is a specific TS inhibitor, can be a substitute to 5FU asit has been demonstrated equivalent in an European trial (6), however it has been found inferior to 5FU modulated by folinic acid in term of overall survival and time to progression in the American trial which used higher and more toxic doses at its initiation.

– *the new drugs advent* : Since few years new drugs active on targets different from TS have been developped in colorectal cancer like oxaliplatin, LOHP (Eloxatine®) (7) and irinotecan, CPT11 (Campto®) (8).
– *Oxaliplatin* (LOHP) is a datch-platin which is active in colorectal cancer with a 24% response rate when used in first line chemotherapy ; combined to 5FU and folinic acid (FOLFOX regimens) it doubles the response rate (9) and seems to increase the possibility of secondary resections (l0).
– *Irinotecan* (CPT 11) is a topoisomerase I inhibitor active in first line chemotherapy (response rates : 18 to 32%). It can be administrated weekly or every 2 or 3 weeks. It has demonstrated its activity after failure to 5FU in term of overall survival and quality of life. In a recently reported trial presented at the ASCO 1999 meeting a [CPT 11 — infusional 5FU — folinic acid] combination was demonstrated superior in term of response rate as well as on survival in first line chemotherapy to infusional 5FU — folinic acid (proc ASCO 1999 ; 1 8 : 233a # 899). In an American trial it was demonstrated superior to bolus 5FU modulated by folinic acid and to CPT11 monotherapy using a weekly schedule (proc ASCO 1999 ; 18 : 233a # 898).

For the future combinations of oral 5FU prodrugs and oxaliplatin or irinotecan will be studied and will

contribute to render more easy and active poly-chemotherapies which will be for many patients suffering from PC the best choice in first line treatment.

Characterisation of the tumor biology will also play an important role for the selection of the best drugs to be used as illustrated by some recent studies (11).

Conclusion

The medical treatment of peritoneal carcinomatosis and especially chemotherapy plays an important role in the management of the patients with PC.

In some patients having an excellent response to CT it may favored secondary surgery but the benefit of this strategy has never been clearly demonstrated.

A randomized multicentric randomized trial (D Elias) is ongoing and compares a combine treatment (surgical excision + local intraperitoneal chemotherapy) plus systemic chemothera,py to systemic chemotherapy alone.

The classical poor prognosis and the multiple therapeutic options underline the need for a multidisciplinary approach to offer the best chance of survival for patients suffering from peritoneal carcinomatose.

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