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Editorial

Of course HIPEC works, but just not for all peritoneal diseases and not with everyone!

In 1990, when CG Moertel published the positive effect of 5-FU Levamisole on the reduction of recurrences after colon cancer surgery, he had persevered even after fifteen years of failure [1]. Indeed, in this work, more than half of the study is negative. Of course, one arm of this study is represented by patients receiving only Levamisole and their survival was not modified compared to the control arm that had only surgery. But the study was also negative for patients who did not have lymph node involvement identified on the colectomy specimen. And yet, practices had just changed, permanently. And for the first time ever, an adjuvant therapy was validated in digestive cancer. So a study does not have to be totally positive to bring in changes in practice.

I was a young Fellow at that time, and for surgeons it had been a revolution. Before that a surgeon could talk with the patient about a tumor but never use the word cancer. After the study, it became impossible to propose a chemotherapy without using the word cancer.

It is therefore very strange that another adjuvant treatment has so much difficulty, to see its importance recognized and especially to be offered to patients. The question posed is whether after resection of peritoneal metastasis, using a cytoreductive surgery, can we administer an adjuvant treatment immediately, in the operating room, as Hyperthermic Intraperitoneal Chemotherapy (HIPEC)?

HIPEC is the subject of many comments and attitudes, often far from the reality of the biology, literature or practices.

A very recent prospective randomized study, HIPECT4, was reported by Spanish Surgeons during ESMO and ESSO congress, which was immediately received with skepticism and criticism [2]. In that trial HIPEC was proposed after resection of a T4 colonic cancer. The drug used was Mitomycin, that seemed appropriate in view of the failure of same study using Oxaliplatine. The locoregional control (LC) was improved in the HIPEC arm with a 3 years LC rate of 97% vs. 87% ($p = 0.025$). The choice of the primary endpoint, locoregional control, had been one of the major point of criticism because the survival did not change. That criticism could be explained for the interest of radiotherapy in rectal cancer, that did not change survival in many trials. But in case of rectal T4 tumor with a high risk of positive circumferential margin R1 or R2, another treatment is proposed to the patient associated with surgery. Using the same idea, HIPEC could be proposed in case of T4 colonic cancer, associated with a high risk of locoregional recurrence because of peritoneal involvement.

The recent trial HIPECT4 is based on the concept that tumor cells implant during surgical resection of the tumor. In that case the cancer cells are first free in the peritoneal cavity because of the T4 evolution, or cells are spilling during the surgical dissection, as identified and demonstrated in human for gastric cancer [3]. Fibrin deposits on scar zones on peritoneum represent a favorable zone for implantation of free cells as demonstrated in animal models [4,5]. After a limited delay, the cells are isolate in the fibrine and can not be targeted by any chemotherapy because no vessels could reach the tumor, but if the intraperitoneal drug is delivered just after surgery an effect is possible [6].

But, However some results could be considered as negative, including in the case of colon cancer peritoneal metastasis in PRODIGE 7 trial [7]. It could be postulated that the inclusion criteria had been too large and, or that postoperative morbidity decreased the possible benefits. But whatever the reasons is, such protocols had been abandoned and a search for a best compromise between efficacy and security has now become mandatory [8]. It is difficult to understand that “HIPEC did not work” regarding the result of one protocol for one type of disease. HIPEC is not a protocol, it is just a way to deliver intraperitoneal chemotherapy after a cytoreductive procedure.

Moreover, HIPEC had demonstrated a positive effect on ovarian peritoneal metastasis as reported in another recent paper published in 2018. It offered one more year of survival to the lady operated in interval situation after chemotherapy [9]. Another study coming from Korea reported a similar one year improvement in interval cytoreductive surgery [10].

So why such an opposition when different surgeons propose such an advance procedure?

For some practitioners, consider that use of HIPEC induce major morbidity, and has to be rejected for that. But such a decision is based on old results. Actually in recent series the morbidity of HIPEC is limited and the mortality is below 2%. For some others the fact that HIPEC is time consuming and require specific investment is a reason to refuse an innovation that they did not decided to invest in. But it is more and more difficult to explain the reasons to refuse using an that increases, even slightly, survival or for some time without local recurrence. Loco regional treatments need~~s~~ a strong investment for the surgical team and the care structure, but part of the future progress probably requires facing that new challenge.

Declaration of Competing Interest

None.

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