Neoadjuvant chemotherapy *versus* primary debulking surgery in the treatment of advanced ovarian cancer: for and against

Interview to C. Zamagni[1] and S. Mahner[2], P. Harter[3], A. du Bois[3] *by* D. Lorusso[4]

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Introduction

The aim of neoadjuvant chemotherapy (NACT) is to reduce the tumour volume or spread of the disease before the main surgical treatment, and it could possibly make the main procedures easier or less invasive. Although the standard therapeutic strategy for advanced ovarian cancer is a maximum primary debulking surgery followed by chemotherapy, a prospective randomized trial carried out by the European Organisation for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Group demonstrated that NACT followed by interval debulking surgery was not inferior to the standard procedure. This study raised a number of controversies, particularly regarding the quality of debulking surgery. To resolve the questions, an additional randomized trial, the Medical Research Council (MRC) CHORUS trial, was carried out and led to the same conclusion: NACT performs as well as primary surgery in advanced ovarian cancer. However, the results of those two trials must be carefully assessed, because the quality of debulking surgery (21% and 19% of optimal cytoreduction in the primary surgery arm in EORTC and CHORUS trials, respectively) significantly affects survival, and may make the interpretation of the trial results confusing and difficult.

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We will try to clarify the role of NACT *versus* primary debulking surgery by asking the opinions of two leaders in the field representative of the two different treatment strategies.

1. What is, in your opinion, "the best" surgical strategy in patients with stage III–IV ovarian cancer? Neoadjuvant chemotherapy followed by surgical debulking or primary debulking followed by adjuvant chemotherapy?

Pro chemotherapy

After decades of the concept that the primary approach in epithelial ovarian cancer should be the maximum surgery possible [1], the prognosis of patients with stage IIIC–IV ovarian cancer remains poor. The "gold standard" of primary debulking surgery (PDS) is based on Griffith's retrospective analysis [2] and on findings of several retrospective and non-randomized prospective studies; the vast majority affected by relevant selection biases. The definition of "optimal debulking surgery" has changed over time and many, but not all, agree that nowadays it should be considered to be the absence of gross residual tumour [3]. Even the extent of surgical demolitions acceptable to achieve "optimal debulking" is still debated. The absence of macroscopic residual tumour after surgery is associated with significantly better outcome [4]. In a series of Gynecologic Oncology Group (GOG) studies, the rate of complete cytoreduction was 23% in stage III [5] and 8% in stage IV patients [6]. On the other hand, in the two prospective randomized trials of PDS *versus* NACT, the absence of residual tumour after complete debulking surgery was confirmed to be the single most important independent prognostic factor [7, 8].

In our opinion, the best evidence-based treatment strategy for patients with stage IIIC–IV ovarian cancer is PDS, when the goal of "no macroscopic residual tumour" is achievable with surgery that is not so aggressive as to severely impair the quality of residual life. Alternatively, NACT should be the preferred approach, if at surgical

exploration (laparotomic or laparoscopic) performed by an experienced gynaecological oncology surgeon, it is evident that macroscopic residual tumour has to be left, avoiding incomplete tumour debulking. We agree that NACT must not be the substitute for inadequate surgery; on the other hand, the role of surgery should not be over emphasized: what is technically feasible is not necessarily clinically useful. Surgical therapies should be tested in prospective randomized trials in order to replace dogmas based on retrospective and biased data with robust scientific evidence. The prospective, randomized trials approach is the only way to go.

Pro surgery

There is worldwide consensus that patients with advanced stage ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IIB–IV) benefit most from complete gross resection of all visible tumour during PDS, and this is the single most important prognostic factor. Although the only published study comparing primary and interval debulking observed a significantly higher rate of complete resection after interval debulking and three cycles of NACT, it did not lead to improved outcome *versus* primary debulking [8, 9], and so we have no data justifying this approach so far. In our opinion, primary debulking with maximum effort to completely resect all visible disease is the best strategy. We have to bear in mind that every patient not undergoing this approach is withheld potentially curative treatment.

2. What is your personal interpretation of data from the CHORUS and EORTC trials about the role of neoadjuvant chemotherapy?

Pro chemotherapy

The great value of these two trials is that they are prospective and randomized [7, 8]. They both indicate that NACT followed by interval debulking surgery is not inferior to PDS followed by chemotherapy for patients with bulky stage IIIC or IV ovarian carcinoma. Outcome data from the EORTC trial [8] and the CHORUS trial [7] (median overall survival 30 months in former and 24 months in the latter) have intensified the never-ending discussion about the surgical skills of the participating investigators. The cross-study comparison of outcome data from the EORTC trial with those from a single-centre experience [10] is another example of biased methodological approach. In our opinion, the major limitation of the two trials is that the selection criteria for eligible patients were applied differently by the participating centres, thus introducing a confounding variable. However, this is a pragmatic approach that reflects the real clinical world. It is not top level evidence, but it is the best we have, and the evidence in favour of very aggressive ultra-radical PDS is even lower. These trials challenge the concept of PDS as the only valid primary approach to treatment of advanced ovarian cancer in daily clinical practice, and indicate the need for further randomized studies.

Pro surgery

So far, only the EORTC study has been published in full [8]. As mentioned above, the results of this trial do not support the use of NACT as the standard approach. Preliminary results of the CHORUS trial have been presented at American Society of Clinical Oncology (ASCO) 2013 [7]. A common and very important aspect of both trials is that the rate of complete gross resection after primary surgery was <20%, which is alarmingly low. This, together with the very short median duration of surgery (120 minutes), leads us to assume that many patients only received an "open-close" procedure. Specialized and well trained gynaeco-oncologic surgeons should achieve a complete resection rate of at least 50%, often by multivisceral resections that can lead to surgeries lasting multiple hours. Therefore, since we know that complete resection is the most important variable in the equation of optimal treatment strategy in our patients, the real question – whether complete resection after primary debulking or after neoadjuvant therapy is better – has not been fully answered.

3. What is the acceptable percentage of patients that could be treated with neoadjuvant chemotherapy in a referral centre?

Pro chemotherapy

In the 26th FIGO Annual Report [4], the absence of macroscopic residual disease after PDS in 2160 patients with stage IIIC ovarian cancer was 16%. Even in a tertiary referral centre, the proportion of unselected stage IIIC-IV patients with no gross residual tumour after PDS does not exceed 20%, and more than 40% of patients are left with a residual tumour greater than 1 cm after surgery [11]. As a consequence, in an unselected stage IIIC-IV population the percentage of patients that could be treated with NACT is over 40%, even in the most authoritative referral centres.

Pro surgery

Generally, all patients that are physically fit enough to undergo multi-hour, multivisceral surgery should be offered primary debulking. There are, however, some patients (for

example, those who die within 6 months after initial diagnosis despite adequate treatment) who, retrospectively, do not benefit from this approach. They cannot be identified prior to therapy yet, but in this population, either interval debulking after neoadjuvant therapy, or probably no surgery at all and primary chemotherapy, might be the better approaches. A patient who is not physically fit at primary diagnosis (e.g. with acute pulmonary embolism) would undergo neoadjuvant chemo and interval debulking in our centres. But these are less than 5% of the whole population.

4. How do you select patients for neoadjuvant chemotherapy? In your opinion, what are the preoperative or intraoperative criteria that suggest patients should have neoadjuvant chemotherapy in your centre? What is the role of laparoscopy in evaluating surgical cytoreduction?

Pro chemotherapy

In our centre, all the cases are discussed by a multidisciplinary dedicated team (gynaecologist oncologist, medical oncologist and pathologist). We agree that in most cases, the preoperative imaging studies are not sufficiently reliable to predict surgical outcome in patients with advanced ovarian cancer. Laparoscopy has an excellent positive predictive value (PPV) for predicting suboptimal cytoreduction [11]. As a consequence, except for those few women who are clearly not suitable for debulking surgery at CT scan, prior to selection for NACT, all other patients in our centre undergo an open laparoscopy in order to document the impossibility of complete primary cytoreduction.

Pro surgery

Preoperative criteria have been mentioned in the previous reply. Intraoperatively, there are no criteria for submitting patients to NACT. The GOG study [12] demonstrated that additional surgical resections after NACT did not result in improved outcome if the primary approach was not successful despite optimal infrastructure (i.e. experienced surgeons in a specialized centre). If this prerequisite is not fulfilled and a patient is coincidentally operated on, the next step should be referral to a specialized centre, not NACT. Minimal invasive surgery is an intriguing tool for assessing operability. Unfortunately, so far, no clearly defined assessment techniques have been established. In addition, the decision not to perform laparotomy – and possibly attempt debulking based on laparoscopy – would mean to deny the patient potential curative surgery.

5. What is the most appropriate number of neoadjuvant chemotherapy cycles?

Pro chemotherapy

The two phase III randomized trials comparing PDS *versus* NACT used three cycles of preoperative chemotherapy and this should be considered the standard when NACT is offered to patients in daily clinical practice [7, 8]. However, the optimal duration of NACT remains to be defined and it is very unlikely that the maximum possible advantage from NACT can be obtained by such a short-term treatment. The Bristow and Chi meta-analysis showing that each incremental chemotherapy cycle after the third cycle of NACT resulted in a 4.1-month decrease in survival, must be definitively ignored because of its methodological limitations as recognized by the Authors themselves [13]. In a meta-analysis conducted on the same 21 studies evaluated by Bristow and Chi, in which the random-effect meta-regression was more properly used instead of a simple linear regression [14], the detrimental effect of increase number of NACT cycles was not confirmed, indicating that the allocation of poorer prognosis patients to NACT and to a greater number of chemotherapy cycles is a general phenomenon in non-randomized studies, leading to a severely confounding selection bias. In order to investigate the optimal duration of NACT, we are conducting a phase II–III randomized trial (GOGER 01) that compares three *versus* six cycles of carboplatin-paclitaxel NACT in stage IIIC–IV ovarian cancer patients not suitable for optimal cytoreduction (defined as no macroscopic residual tumour).

Pro surgery

Since every phase III study evaluating this approach used three cycles, this should be followed.

6. In the standard treatment algorithm for stage IIIB–IIIC and IV ovarian cancer, does the introduction of bevacizumab modify the surgical approach and, if so, how?

Pro chemotherapy

In my opinion, there is no reason why the introduction of bevacizumab should modify the treatment strategy for ovarian cancer patients. The patients treated with NACT should receive bevacizumab after surgery.

Pro surgery

Bevacizumab is applied after surgery during first-line therapy. Therefore, it does not modify the surgical approach.

7. What are your opinions on the optimum treatment of stage IV disease (please specify pleuric, hepatic or supradiaphragmatic lymph nodes, or pulmonary disease) – neoadjuvant chemotherapy or surgery?

Pro chemotherapy

As I answered question 1, in our practice, only patients with oligometastatic completely resectable stage IV ovarian cancer are proposed for PDS. In our centre, the presence of pleural effusion with positive cytology as the only metastatic site is not a reason for inoperability, while mediastinal and supraclavicular lymph node metastases are, and these latter patients are offered NACT. In all other cases in which complete cytoreduction is not feasible, NACT is the preferred strategy.

Pro surgery

We know that complete resection at primary surgery substantially improves the outcome of patients with FIGO stage IV disease (irrespective of the localization).

We have no evidence that the same holds true for interval debulking. Therefore, every patient, even those with suspected FIGO IV disease, should undergo the standard approach of primary surgery.

8. In your centre, what are the intraoperative criteria for "no cytoreduction"?

Pro chemotherapy

The criteria for inoperability (defined as no possibility of achieving no gross residual tumour) in our centre are a Fagotti's score ≥8, neoplastic involvement behind the porta hepatis or around the superior mesenteric artery, deep infiltration of the radix mesenterii of the small bowel, multiple intrahepatic metastases, or serosal invasion necessitating extensive bowel resections with a strong negative impact on quality of life or multiple extra-abdominal metastases.

Pro surgery

If maximum surgical effort cannot result in residual tumour <1 cm, prognosis cannot be improved. Therefore, the patient should be spared any resections and undergo primary chemotherapy.

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