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EDITORIAL

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Neoadjuvant chemotherapy in the management of cervical cancer. A long and winding road. State of the art

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Cervical cancer is a concerning issue in our country for it is the second most common gynecologic malignancy in women aged 45 to 50, and the incidence is increasing among young women.

The incidence in Argentina is estimated at 30.4 cases per 100,000 women with 5500 new cases diagnosed and 2000 deaths reported yearly. Of all the cases diagnosed, 56% to 77% are already in a locally advanced stage [1–4].

The HPV types most commonly found are 16-18-31-33-35-45-56. Among the histological types, the squamous type (85–90%) prevails over adenocarcinoma (5–15%) [1–4]. The prognostic factors for the disease include FIGO (Federation International of Gynecology and Obstetrics) advanced stage, bulky disease, the presence of positive lymph nodes, the histological grade and lympho-vascular invasion [4].

From the mid 30's to the mid 80's no changes in survival rates were reported for the different cervical cancer stages regardless of the treatment options available then (radiotherapy or surgery). Later, the introduction of chemotherapy for the primary treatment of cervical cancer represented a milestone in the history of the disease.

The advantages of the implementation of neoadjuvant chemotherapy include the reduction of both the size and spread of the tumor, increased resectability and ease of radiation therapy administration, as well as the management of remote micrometastases. The disadvantages include the potential development of chemo-resistant clones and delay in the curative treatment. However, these factors have been found to be relative [5].

FIGO (2003) [6] proposed the use of neoadjuvant chemotherapy as a treatment option, and called it "Buenos Aires Scheme", which was a rapid VBP (vincristin, bleomycin and cisplatin) chemotherapy scheme, administered every 7 to 10 days:

- Cisplatin 50 mg/m^2 (day 1).
- Vincristine 1 mg/m^2 (day 1).
- Bleomycin 25 mg/m^2 (days 1, 2 and 3).

In our pioneering experiencein Argentina, in the first three prospective randomized trials at international level, Sardi *et al.* [5, 7, 8] of the Gynecology Course at the University Teaching Hospital in Buenos Aires evidenced the following:

- Increased overall response and disease-free survival in stage Ib1.
- Increased resectability in stages Ib2 by 85 to 100%; and between 52 and 80% in stages IIb.
- In general, non-responders (chemoresistant patients) have a poor prognosis (14%) in both groups, in which case surgery might be a better option.
- Decrease of the elevated pathological risk factors in the group receiving neoadjuvancy.

Increasedsurvival:

- Stage Ib2: 80% *vs.* 61% (neo + surgery *vs.* surgery).
- Stage IIb: 64% *vs.* 50% (neo + surgery *vs.* radiotherapy or surgery) − neoadjuvant chemotherapy + radiotherapy (RT) 56% *vs.* 50%.
- Stage IIIb: 37% neo + surgery *vs.* 23% RT, neo + RT 36% *vs.* 23% RT.

In those trials, there were included non-selected patients.

Several trials on the use of chemo-neoadjuvancy for the management of cervical cancer have been conducted [9, 10].

A randomized, multicenter Italian trial published in 2002 [11] reported that the cohort of patients in stage Ib2 to IIb benefited in terms of overall survival and disease-free survival thanks to neoadjuvant chemotherapy followed by radical surgery, as compared to those patients who received radiotherapy alone.

In 2003, the Cochrane Group [12] published a systematic review and a meta-analysis based on the individual data of patients conducted in order to assess the effect of neoadjuvant chemotherapy. Data from 18 randomised trials and 2074

non-selected patients were collected, comparing Neoadjuvant Chemotherapy + radiotherapy *vs.* radiotherapy alone as well as Neoadjuvant Chemotherapy + surgery *vs.* standard radiotherapy.

The Hazard Ratio (HR) in this review was 0.65, with a 35% reduction of the risk of death, and an increased survival rate of 14%. Moreover, a 32% reduction of the risk of pelvic recurrence was observed. Also, the authors concluded that a maximum tolerable dose of cisplatin (>25 mg/m^2) in short cycles (<15 days) must be used, in this meta-analysis.

In 2006, Choi-Kim *et al.* [13] published a study supporting the therapeutical benefit of neoadjuvant chemotherapy associated to radical surgery in patients with bulky cervical cancer in stages Ib and IIA. In the case of chemoresistance, it was considered that these patients would also be radioresistant, and surgery was left as the last best treatment option, even more in stage IIb patients. Consequently, the resistant clones would be removed favoring second line therapies. These concepts had already been described by Sardi *et al.* [5, 14] back in 1997/98 in a prospective randomized trial on stage IIb disease.

According to the "Back to the future effect" in 2012, a collaborative international meta-analysis conducted by the Cochrane Group [15] on the efficacy of neoadjuvant chemotherapy in FIGO stage Ib to IIA patients concluded that neoadjuvancy prior to surgery reduces the need for adjuvant radiotherapy as it decreases tumor size and both lymph node and distant metastases.

In 2013, Kim-Sardi *et al.* [16], in another meta-analysis stated once again that in stages Ib under 4 cm with complete pathological response the use of neoadjuvant chemotherapy followed by surgery leads to better locoregional control of the disease, with a statistically significant reduction in local recurrence. So, less radical surgeries may be performed, including fertility sparing procedures, concepts which had also been described by Sardi *et al.* [5] in 1997.

Going back to the "Back to the future effect" in 2017, Chou *et al.* [17] and other authors [18, 19] also published reports on the increased doses and dosage between weekly paclitaxel and cisplatin cycles followed by radical hysterectomy in stages Ib2 and IIA2 cervical cancer (rapid scheme/dense doses). That is, maximum tolerable dose in short cycles (let's not forget the rapid VBP, its predecessor).

A weekly treatment for 3 cycles was indicated with excellent short-term results, with the caveat of a small sample, this study, however, supports future phase II trials.

In 2016 [20] the SGO (Society of Gynecologic Oncology) supported the new ASCO (American Society of Clinical Oncology) cervical cancer clinical practice guidelines, including treatment recommendations adapted to resource availability. In areas where patients are not able to receive radiotherapy, extrafascial hysterectomy, whether alone or after neoadjuvant chemotherapy, may be an option for women with stage IA1 or IVA cervical cancer.

Radiotherapy and chemotherapy administered simultaneously are the standard in improved or maximum care settings for women with stage Ib to IVA disease. The panel underlines the use of low dose chemotherapy during radiotherapy but not at the expense of delaying radiotherapy if chemotherapy is not available in settings with limited resources for care.

In the protocol of the EORTC (European Organization for Research and Treatment of Cancer) 55994 trial [21], 620 patients in FIGO stages Ib2–IIb were randomized to neoadjuvant chemotherapy followed by surgery with concomitant chemoradiotherapy, and the overall survival rate was similar in both groups.

No doubt, neoadjuvant chemoradiotherapy opened many doors:

- The extremism in the surgical management to perform ultraconservative [5, 22–28] and even ultraradical surgeries [29–32].
- What to do after neoadjuvant chemotherapy. For example, the chemotherapy-surgery-chemotherapy sandwich scheme published by Sananes *et al.* [33] in 1998, and later by Angioli *et al.* [34] in 2006.
- What to do with bulky tumors (>4 cm) in stages IIb and IIIb. For example, neoadjuvant chemotherapy followed by chemoradiation (McCormack, 2013–2023) [35, 36]. Soderini *et al.* [37] and Aragona *et al.* [3] 2018 Depietri *et al.* [38] 2022, proved that overall survival drops dramatically in central tumors >6 cm and year by year, showing the need of an additional chemotherapy treatment previous to chemoradiation. At this point, the Interlance study [36], that included five hundred randomised patients, demonstrated that neoadjuvant chemotherapy followed by chemoradiation is statistically significative better than chemoradiation alone, in terms of disease free and overall survival rates for those locally advanced cervical cancers, becoming this modality as a new standard o treatment.

It is important to remark that, in FIGO staging system, the lymph node status was not taken into account until 2018, by imaging or surgical procedures [39]. It was also reconsidered the central tumor size, introducing the new Ib2 stage for measures >2 and <4 cm; where neoadjuvant chemotherapy could benefit surgical fertility sparing procedures or less radical treatments [27, 28, 39].

The arrival of different target therapies added before (neoadjuvant) to standard treatments, could be a new and very next future in this field [40, 41].

No doubt, with such a large body of evidence, with more than 1000 papers in favor of neoadjuvant chemotherapy, the question then is "why are we still discussing this topic?". This discussion ended in IGCS (International Gynecological Cancer Society) 2019 with the presentation of the EORTC 55994 protocol [21] at the neoadjuvant chemotherapy in cervical cancer symposium [42] and its inclusion in the NCCN (National Comprehensive Cancer Network) guidelines in 2021 [43].

After more than 35 years of expertize, constant innovation, perseverance and search for excellence in the management of cervical cancer, we can say the neoadjuvant chemotherapy plays an important role and must be considered one of the standard treatment options in locally advanced cervical cancer.

The most important points to remember appear below:

1. Tailoring treatment for each particular patient.
2. The concept and the reason why we do this matter more than the drug used, for the drug will certainly change and improve in time.
3. Which is the best chemotherapy scheme? The one with:

- The best response rate

- The least toxicity
- The quickest way to be carried out
- Ability to deliver in day unit/ambulatory care setting
- The cheapest cost
- Up to now, it is best to try to use maximum tolerable doses and short duration platinum-based chemotherapy.

4. The concept of adding toxicities of treatments (chemotherapy + surgery + radiotherapy), is a relative truth and a kind of point of view because we are treating mostly Locally advanced tumors, that need much more than one treatment for being control or cure.

5. No women should die of cervical cancer in the XXI century. Cervical cancer is a preventable disease that can be diagnosed early on and treated accordingly by specialists in the field.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AS—wrote and designed the kind of the study. NB, FAA, IMM and AA—contributed in the search of references and also contributed for the writing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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