Proceedings of Experts Workshop on Cervical Cancer
Vienna - November 23, 2002

The role of neoadjuvant chemotherapy followed by radical surgery in the treatment of locally advanced cervical cancer

P.L. Benedetti-Panici, *M.D.*; **M.A. Zullo,** *M.D.*; **L. Muzii,** *M.D.*; **N. Manci,** *M.D.*; **F. Bellati,** *M.D.*; **F. Plotti,** *M.D.*; **S. Basile,** *M.D.*; **R. Angioli,** *M.D.*

Department of Gynecology, Campus Bio-Medico University, Rome (Italy)

Summary

In 1984 the first pilot study on neoadjuvant chemotherapy in cervical cancer was reported. Since then, many investigators have studied the possible role that this therapeutic strategy could achieve in patients. Different chemotherapic combinations are constantly being attempted in order to obtain the maximum tumour response. At the same time few randomised studies have demonstrated the superiority of this treatment when adopted before radical surgery, in terms of overall survival compared to radiotherapy alone. Recently a detailed meta-analysis has been performed and the results confirmed what previously was achieved by the randomised trials. Since the beginning of all the phase III trials, the standard treatment of locally advanced disease has been modified from radiotherapy alone to concomitant radio-chemotherapy. For this reason the EORTC group has launched a trial with the objective of comparing neoadjuvant chemotherapy followed by radical surgery versus concomitant chemo-radiotherapy.

Key words: Neoadjuvant chemotherapy; Cervical cancer; Radical surgery.

Introduction

It has been demonstrated that cervical cancer is a chemosensitive tumour. The first pilot study that had as a primary objective the evaluation of CT in a neoadjuvant setting was reported by Friedlander in 1984 (1). Neoadjuvant chemotherapy (NACT) has been adopted both before surgery and radiotherapy (RT). The ladder has failed to demonstrate any significant benefit in phase III trials. We are going to review the use of chemotherapy as a neoadjuvant treatment followed by radical surgery (RS) in cervical cancer.

Rational

The rationale for the use of neoadjuvant chemotherapy is listed in Table 1. The most important advantage of primary chemotherapy is tumour size reduction. Large size tumours distort pelvic anatomy and this causes difficulties to radiotherapists and surgeons [2, 3].

This reduction in size increases radio-sensitivity by reducing the number of cells and by reducing hypoxic cell traction [4-6]. Some regimes, especially platinum-based ones, also act directly as radiation potentiators [7, 8]. In addition NACT allows a precocious and more successful treatment of microscopic distant metastases [4, 6].

This can be partially justified by the more aggressive regimes that can be adopted in previously untreated patients. These patients usually have an intact bone marrow reserve and nephro-ureteral system. Finally drug distribution is more favorable in non iatrogenically damaged tissue.[6, 9].

On this basis, clinical studies were started and are still being carried out with the primary objective of delineating the real effect that NACT can have in these patients.

Pilot studies

Until 1983 cervical carcinoma was considered a chemo-resistant cancer, therefore chemotherapy was only used after other treatment modality failure. Friedlander *et al.* [10] were the first to investigate the effect of chemotherapy on cervical cancer in previously untreated patients in 1983. This pilot study included ten out of 33 assessable patients with locally advanced inoperable disease who underwent chemotherapy with three courses of vinblastine, bleomycin and cisplatin (VBP) as a first line treatment. Six (60%) of the these patients obtained a partial response to chemotherapy; seven (70%) out of nine who proceeded treatment with radiotherapy, obtained a complete clinical response after completation of treatment. Based on this preliminary report, the same authors conducted the first pilot study finalized to evaluate the role of NACT before radical surgery in the treatment of advanced cervical carcinoma (FIGO Stage IB -

Table 1.

Rationale of neoadjuvant chemotherapy
Reduces tumour size
Acts on well vascularized tissue
Used on intact bone marrow
NACT may reduce postoperative micrometastasis progression
Acts against local and distant subclinical metastasis
Acts as a prognostic factor
Acts as a radiation potentiator
Increases radisensitivity by improving size reduction and decreasing hypoxic cell fraction
Reduces pelvic distortion by tumour mass and facilitates subsequent RT
Turns inoperable tumours into resectable
Guides therapeutic itinerary: identifies chemosensitive tumors

With permission from: P.L. Benedetti-Panici, R. Angioli: "Neoadjuvant chemotherapy in cervical cancer". In: "Chemotherapy for Gynecologic Neoplasms: Current Therapy and Novel Approaches" (in press).

IVA) [1]. This study confirmed the high proportion of partial clinical responses that could be achieved and it showed a 17% complete clinical response rate after only chemotherapy. In all patients with complete clinical response who underwent surgery, microscopic foci of cancer were found.

Several pilot studies are verifying the efficacy of different drugs both as single or in combination regimens. The majority of the authors agree on the necessity to adopt a platinum-based combination. This drug alone or in combination has demonstrated the highest clinical response rate. An important issue is the total drug dose to be administered and the dose intensity. Valle *et al.* [11] were obliged to reduce the overall drug dose from adriamicyn 50 mg/mq, bleomycin 10 mg/mq and cisplatin 100 mg/mq to adriamicyn 50 mg/mq, bleomycin 6 mg/mq and cisplatin 50 mg/mq due to unacceptable toxicity but were anyhow able to demonstrate good tumour response. Sardi *et al.* used two different dose intensity regimens on patients with Stages Ib to IIIb composed of three cycles of VBP [2]. The conventional VBP scheme was composed of: vinblastine 1 mg/mq, bleomycin 15 mg/mq on day 1 to 6 and cisplatinum 50 mg/mq with an interval between doses of 21 days. The modified VBP scheme was composed of: vinblastine 1 mg/mq, bleomycin 25 mg/mq on day 1 to 3 and cisplatinum 50 mg/mq with an interval between doses of ten days. The overall bleomycin dose was reduced from 90 mg/mq to 75 mg/mq in every cycle in favour of an important increase in dose intensity in the modified regime. Tumour response in different sites was different for the two regimes; the conventional scheme achieved a moderate response in the cervix and vagina (62.5%) but a poor response in the parametrium (28.5%) compared with the modified scheme which obtained a high response rate in all regions (92% and 94%, respectively). No major toxicity occurred in the high-dose intensity group.

These observations allowed other authors to adjust doses and administration intervals. Benedetti-Panici *et al.* were the first to apply dose intensity regimes as neoadjuvant treatment [12]. The schedule adopted was cisplatin 40 mg/mq for five consecutive days, with bleomycin 15 mg IV bolus on days 1, 2, 8 and 9. This work demonstrated the feasibility of a high-dose intensity cisplatinum and bleomicin regimes with the advantage of a great reduction of the time interval before definite treatment as well as a reduction of overall treatment duration.

In 1987, Kirsten [13] published the update of the first NACT pilot study, previously reported by Friedlander *et al.* on patients with Stage Ib to IVa [1]. This study demonstrated the important role that central tumour (cervix) response has as a prognostic factor. Central tumour responders have, compared with non responders, a higher rate of disease recurrence (81% vs 35%), radiotherapy failure (80% vs 21%) and shorter median post-chemotherapy survival (117 weeks vs 45 weeks). In fact, other studies from the mid 80's also showed how NACT seems to affect the rate of lymph node metastasis. Patients who have undergone NACT have a reduced rate of lymph node involvement [14]. In particular, patients with better central response were less likely to have lymph node metastasis [15-18]. Therefore it is rational to believe that tumours that respond in the cervix, also respond in lymph nodes [12, 15-17, 19, 20].

Important prognostic factors have been identified in these patients. The most important is response to NACT. Other prognostic factors are cervical depth of invasion and parametrium involvement. The importance of tumour grading and histotype are still debated [12, 20]. The analysis conducted on survival in the pilot study conducted by Benedetti-Panici *et al.* showed a relative risk of 2.46 in poorly differentiated tumours compared with good and moderate ones (1.33-4.53, 95% confidence interval) [21]. Most of the above-mentioned studies were conducted on squmous cell carcinomas but results on adenocarcinomas have demonstrated similar results [21, 22].

In 1990, an update of an Argentinian pilot study was published. The extensive number of patients allowed some important considerations to be made. The response rate to NACT was inversely proportional to tumour stage. Overall response rate in patients with Stages IIB was 92% and in Stage IIIB 73% [4]. This is probably due to the different tumour size [20, 23]. The number of patients with no evidence of disease (NED) after two years was much higher for Stage IIB compared with Stage IIIB. This study included a historical control group treated with RT. The percentage of patients with NED after two years was significantly higher in the NACT group. This advantage of NACT in the disease-free survival (DFS) rate was more important in Stage IIB (79% vs 47%, $p < 0.01$) but a significant difference was also present even in patients with Stage IIIB disease (50% vs 26%, $p < 0.01$) [4].

These immature results have partially been confirmed by the analysis reported on the long-term survival that was done on 128 patients who entered the NACT pilot studies conducted by Benedetti-Panici *et al.* between 1986 and 1990 [21]. The estimated 10-year survival rates were 91%, 80%, and 34.5% for Stage IB2-IIA bulky, IIB and III, respectively ($p < 0.001$). The 10-year disease overall disease-free survival (DFS) estimate rate is 75%.

Randomised studies

Most randomised trials have compared patients undergoing NACT with a control group treated with radiotherapy. Three different therapeutic techniques were examined with NACT: NACT followed by RT, NACT followed by RS (with or without adjuvant RT on the basis of pathologic risk factors), and NACT followed by RS followed by adjuvant RT.

The first trial evaluated NACT followed by RT. Souhami et al. analysed the effect of this strategy on patients with Stage IIIB disease [5]. Clinical response rates were high, but survival in the experimental arm was sufficiently low to have the study suspended precociously. Five-year survival analysis demonstrated an overall survival (OS) of 23% and 39% in the NACT-RT and RT control group, respectively.

Kumar *et al.* reported a study in which they enrolled 184 patients. After the completion of radiotherapy, the complete response rate in the NACT group was 70%. Chemotherapeutic responders obtained an 83% complete clinical response after RT vs 33.3% obtained in the chemotherapeutic non responders. There was no statistical difference in overall survival between the two groups: 38 vs 43% in the NACT-RT and the RT group, respectively, even though the trend was in favour of only radiotherapy [24].

A more precise description of randomised trials has been recently reported by Benedetti-Panici *et al.* [25].

Much more encouraging are the results obtained by the use of NACT before radical surgery. Two large studies have been performed using NACT + RS without routinely administered adjuvant RT, the one published by Chang TC et al. in 2000 and one performed by Benedetti-Panici P. *et al.* presented in 2002. The former included 120 patients with Stage Ib2 or bulky Stage II disease randomly assigned to the experimental (NACT + RS) or the control arm (RT). Disease-free survival (DFS) and overall survival (OS) showed no significant difference at five years, the ladder being of 70% and 62% in the NACT and control arm, respectively [26].

The second one was a multicenter randomised trial conducted by 14 Italian centres. Out of 409 patients, 210 were assigned to NACT followed by a RS arm. Eligible patients were those with squamous cell carcinoma and disease Stage Ib2, IIa > 4 cm, IIb and III. Survival analyses were conducted on intention to treat, eligible patients and patients receiving treatment according to the protocol. In all these groups a significant increase in 5-year OS and DFS was observed. These results were confirmed in the analysis by FIGO stage for Stages Ib2-IIa, but not for Stages IIb and III. In particular, the 5-year survival analysis by FIGO stage showed significantly longer overall survival 64.7% vs 46.4% ($p = 0.005$) and progression-free survival 59.7% vs 46.7% ($p = 0.02$) for the Stage Ib2 to IIb patients in the NACT arm compared with the RT arm, respectively. Survival rates for Stage III patients did not significantly differ in the two arms (OS 41.6% vs 36.7% $p = 0.36$; DFS 41.9% vs 36.4% $p = 0.29$).

Sardi *et al.* [27-29] investigated the use of NACT followed by RS and additional adjuvant radiotherapy.

They reported three studies on NACT followed by RS followed by RT. The effect of this treatment modality was conducted on patients with Stage IB, IIB and IIIB disease [27-29].

Concerning Stage IB tumours, NACT did not significantly affect the outcome in terms of 8-year OS (82% vs 77% in the NACT and control group, respectively). Patients in the experimental arm achieved a significantly higher respectability (100 vs 85% $p < 0.001$). This trial began before the introduction in the staging system of the distinction between bulky and no bulky disease.

The investigation on Stage IIB tumours included four arms: RT, RS + RT, NACT + RT, NACT + RS + RT [28]. The group treated with NACT followed by RS and RT enrolled 76 patients. This group had the highest survival rate of the four arms and this difference was significant when compared to the two control groups. In particular, survival was 41% and 48% in the RS + RT ($p < 0.01$) and RT ($p < 0.005$) arm, respectively, compared to 65% in the NACT + RS + RT group. Patients who underwent NACT had a higher resectability rate and better pathological risk factors. The OS analysis in the two surgically treated arms in regard to initial tumour size, demonstrated a benefit of NACT both in tumours with an initial dimension greater (73% vs 51%) and lesser (53% vs 33%) than 5 cm.

Concerning the Stage IIIB tumours, Sardi *et al.* demonstrated that OS was better in patients treated with NACT independently from the adjuvant treatment that followed. The 4-year OS survival was 63%, 53% and 37% for patients treated in the NACT + RS, NACT + RT and RT control group, respectively. No significant difference was revealed between the two experimental arms, but both had significantly better results compared to the control group ($p = 0.025$ for NACT + RS vs RT and $p = 0.005$ for NACT + RT vs RT). Similar results were obtained for the DFS. Other parameters that gained significant benefits from NACT compared to the control group, but with no significant difference between the two different adjuvant treatment arms, were presence of hydronephrosis and unilateral extension to the pelvic wall [29].

Recently a meta-analysis compared NACT followed by RT or RS vs RT.

The results demonstrated a possible benefit of NACT followed by RT if high dose intensity of cisplatin was adopted. In addition the meta-analysis demonstrated a benefit of NACT followed by RS versus RT. The limited number of patients analysed did not allow other subgroup considerations. This analysis supports the tendency that gynaecologic oncologists have acquired in these years to adopt short, high-dose intensity chemotherapic regimens [30].

A more complete review on the randomised trial has been described by Benedetti-Panici *et al.* [25].

Conclusions

In conclusion, cervical cancer is a chemo-sensitive tumour. Various regimes have been studied but there is no unanimous approval for which one is the gold standard, although most of the studies have adopted a platinum-based regimen. Neoadjuvant chemotherapy has shown to be effective in decreasing tumour size and increasing operability of large tumours. When used before radical surgery it has given better results than RT alone, especially in Stage IB2-IIB tumours.

References

[1] Friedlander M.L., Atkinson K., Coppleson J.V., Elliot P., Green D., Houghton R. *et al.:* "The integration of chemotherapy into the management of locally advanced cervical cancer: a pilot study". *Gynecol. Oncol.,* 1984, *19* (1), 1.
[2] Sardi J.E., di Paola G.R., Cachau A., Ortiz O.C., Sananes C., Giaroli A. *et al.*: "A possible new trend in the management of the carcinoma of the cervix uteri". *Gynecol. Oncol.*, 1986, *25* (2), 139.
[3] Benedetti-Panici P., Greggi S., Colombo A., Amoroso M., Smaniotto D., Giannarelli D. *et al.*: "Neoadjuvant chemotherapy and radical surgery versus exclusively radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multi-centre randomised study". *J. Clin. Oncol.,* 2002, *1*, 20 (1), 179.
[4] Sardi J., Sananes C., Giaroli A., Maya G., di Paola G.: "Neoadjuvant chemotherapy in locally advanced carcinoma of the cervix uteri". *Gynecol. Oncol.,* 1990, *38* (3), 486.
[5] Souhami L., Gill R.A., Allan S.E., Canary P.C.V., Arauio C.M.M., Pinto L.H.J., Silveira T.R.T.: "A Randomized trial of chemotherapy followed by radiation therapy in stage IIIB carcinoma of the cervix". *JCO,* 1991, *9* (6), 970.
[6] Eddy G.L.: "Neoadjuvant chemotherapy before surgery in cervical cancer". *J. Natl. Cancer Inst. Monogr.*, 1996, (*21*), 93.
[7] Douple E.B., Green C.J., Simic M.G.: "Potentiation of cellular radiosensitivity by nitroprusside and vitamin B12". *Int. J. Radiat. Oncol. Biol. Phys.,* 1980.
[8] Muss H.B., Jobson V.W., Homesley H.D., Welander C., Ferree C.: "Neoadjuvant therapy for advanced squamous cell carcinoma of the cervix: cisplatin followed by radiation therapy-a pilot study of the Gynecologic Oncology Group". *Gynecol. Oncol.,* 1987, *26* (1), 35.
[9] Tokuhashi Y., Kikkawa F., Ishikawa H., Tamakoshi K., Hattori S., Matsuzawa K. *et al.*: "Distribution of platinum in human gynecologic tissues and pelvic lymph nodes after administration of cisplatin". *Gynecol. Obstet. Invest.*, 1997, *44* (4), 270.
[10] Friedlander M., Kate S.B., Sullivan A., Atkinson K., Elliott P., Coppleson M. *et al.*: "Cervical Carcinoma: A drug-responsive tumour-Experience with combined cisplatin, vinblastine, and bleomycin therapy". *Gynecol. Oncol.,* 1983, *16,* 275.
[11] Valle J.C., Rezenende M.R., Werneck C., Chu C., Figueredo E.: "Neoadjuvant & adjuvant chemotherapy with adriamycin, bleomycin & cisplatin (ABC) and modified radical hysterectomy in the cancer of cervix, Stage III". Proc. *ASCO*, 1985 (*4*), 125, C-486.
[12] Benedetti-Panici P., Scambia G., Baiocchi G., Greggi S., Ragusa G., Gallo A. *et al.*: "Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. Prognostic factors for response and survival". *Cancer,* 1991, *15*, 67 (2), 372.
[13] Kirsten F., Atkinson K.H., Coppleson J.V., Elliott P.M., Green D., Houghton R. *et al.*: "Combination chemotherapy followed by surgery or radiotherapy in patients with locally advanced cervical cancer". *Br. J. Obstet. Gynaecol.,* 1987, *94* (6), 583.
[14] Kim D.S., Moon H., Kang K.J.: "Primary chemotherapy and postoperative adjuvant chemotherapy in the treatment of squamous cell carcinoma of the uterine cervix". *Gynecol. Oncol.,* 1985.
[15] Kim D.S., Moon H., Hwang Y.Y., Cho S.H.: "Preoperative adjuvant chemotherapy in the treatment of cervical cancer stage Ib, IIa, and IIb with bulky tumor". *Gynecol. Oncol.,* 1988, *29* (3), 321.
[16] Kim D.S., Moon H., Kim K.T., Hwang Y.Y., Cho S.H., Kim S.R.: "Two-year survival: preoperative adjuvant chemotherapy in the treatment of cervical cancer Stages Ib and II with bulky tumor". *Gynecol. Oncol.,* 1989, *33* (2), 225.
[17] Benedetti-Panici P., Scambia G., Greggi S., Di Roberto P., Baiocchi G., Mancuso S.: "Neoadjuvant chemotherapy and radical surgery in locally advanced cervical carcinoma: a pilot study". *Obstet. Gynecol.,* 1988, *71* (3 Pt 1), 344.
[18] Giaroli A., Sananes C., Sardi J.E., Maya A.G., Bastardas M.L., Snaidas L. *et al.*: "Lymph node metastases in carcinoma of the cervix uteri: response to neoadjuvant chemotherapy and its impact on survival". *Gynecol. Oncol.,* 1990, *39* (1), 34.
[19] Dottino P.R., Plaxe S.C., Beddoe A.M., Johnston C., Cohen C.J.: "Induction chemotherapy followed by radical surgery in cervical cancer". *Gynecol. Oncol.,* 1991, *40* (1), 7.
[20] Chang H.C., Lai C.H., Chou P.C., Tseng C.J., Chang T.C., Hsueh S. *et al.:* "Neoadjuvant chemotherapy with cisplatin, vincristine, and bleomycin and radical surgery in early-stage bulky cervical carcinoma". *Cancer Chemother. Pharmacol.,* 1992, *30* (4), 281
[21] Benedetti-Panici P., Maneschi F., Cutillo G., Greggi S., Salerno M.G., Amoroso M.: "Modified type IV-V radical hysterectomy with systematic pelvic and aortic lymphadenectomy in the treatment of patients with Stage III cervical carcinom. Feasibility, technique, and clinical results". *Cancer,* 1996, *1,* 78 (11), 2359.
[22] Zanetta G., Dissoni A., Gabriele A., Bandoni F., Colombo A., Perego P., Mangioni C.: "Intense neoadjuvant chemotherapy with cisplatin and epirubicina for advanced or bulky cervical and vaginal adenocarcinoma". *Gynecol. Oncol.,* 1997, *64,* 431.
[23] Leone B., Vallejo C., Perez J., Cuevas M. A., Machiavelli M., Lacava J. *et al.:* "Ifosfamide and cisplatin as neoadjuvant chemotherapy for advanced cervical cancer". *Am. J. Clin. Oncol.,* 1996, *19* (2), 132.
[24] Kumar L., Kaushal R., Nandy M., Biswual B.M., Kumar S., Kriplani A. *et al.*: "Chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer: A randomised study". *Gynecol. Oncol.,* 1994, *54,* 307.
[25] Benedetti-Panici P.L. *et al.*: "Neoadjuvant chemotherapy in cervical cancer". In: "Chemotherapy in Gynecologic Oncology" (in press).
[26] Chang T.C., Lai C.H., Hong J.H., Hsueh S., Huang K.G., Chou H.H. *et al.:* "Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky Stage IB and IIA cervical cancer". *J. Clin. Oncol.,* 2000, *18* (8), 1740.
[27] Sardi J.E., Giaroli A., Sananes C., Ferreira M., Soderini A., Bermudez A. *et al.*: "Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results". *Gynecol. Oncol.*, 1997, *67* (1), 61.
[28] Sardi J., Sananes C.E., Giaroli A., Bermudez A., Ferreira M.H., Soderini A.H. *et al.*: "Neoadjuvant chemotherapy in cervical carcinoma Stage IIB: a randomised controlled trial". *Int. J. Gynecol. Cancer,* 1998, *8*, 441.
[29] Sardi J., Giaroli A., Sananes C., Rueda N.G., Vicgi S., Fereira M. *et al.*: "Randomized trial with neoadjuvant chemotherapy in Stage IIIB squamous carcinoma cervix uteri: an unexpected therapeutic management". *Int. J. Gynecol. Cancer,* 1996, *6,* 85.
[30] Tierney J.F.: "Neoadjuvant chemotherapy for locally advanced cervical cancer: A systematic review and meta-analysis of individual patient data from 21 randomised trials". Eur. J. Cancer (in press).

Address reprint requests to:
P.L. BENEDETTI-PANICI, M.D., Ph.D.
Via Longoni, 83
00155 Rome (Italy)