

HEMOGLOBIN LEVEL AND NEOADJUVANT CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CARCINOMA

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Summary

Hemoglobin level is a very important prognostic factor in patients with gynecological carcinomas. Anemia in patients with cervical carcinoma occurs frequently and is due to the aggressive biological potential of a tumor as well as because of the poor response of patients to radiation therapy. Chemoradiation is a standard treatment followed by surgery in patients with locally advanced cervical carcinomas. Good overall results after such treatment, good quality of life, and almost no recidivism have established this method as a treatment of choice for patients with locally advanced cervical carcinomas.

Sixty-four female patients with cervical carcinoma underwent neoadjuvant chemoradiation, followed by radical hysterectomy at the Department of Gynecologic Oncology, University Medical Center in Zagreb. The stages of the disease ranged from FIGO stage Ib1 to FIGO stage IIIa. Histopathological findings were squamous cell carcinoma and glandular carcinoma of the cervix. The ECOG performance status was graduated from 0 to 1.

Neoadjuvant chemoradiation regimen included cisplatin (40 mg/m² once a week for 4 weeks) with concomitant radiotherapy (40 Gy total pelvic + brach therapy). Furthermore, the time interval between chemoradiation and surgery was evaluated. Response to chemoradiation therapy was observed, and the hemoglobin level and general conditions (according to the ECOG performance status) were evaluated.

All the 64 patients had chemoradiation therapy prior to radical surgery. The median dosage at point A was 77.28 Gy and the median duration time of chemoradiation was 34.37 days. The time interval from chemoradiation to radical surgery was approximately 34.4 days. Hemoglobin levels decreased from 120.7 to 108.7 g/l at the end of concomitant chemoradiation. The mean tumor diameter was significantly decreased after neoadjuvant chemoradiation, and we classified the results after chemoradiation therapy as complete remission, partial remission, and stabilization of the disease, according to the WHO response criteria with respect to the size of a residual tumor. After chemoradiation and surgery, the hemoglobin level and long-term survival were evaluated.

The correlation between the hemoglobin level and long-term survival after neoadjuvant chemoradiation and radical surgery in patients with different stages of cervical cancer was studied. We found that hemoglobin level could be a prognostic factor, but mostly, along with other prognostic factors, such as ECOG performance status, stage of the disease, dosage at point A, and interval between chemoradiation and surgery. However, we observed that the cellular types of tumor were of no significance.

KEYWORDS: *chemoradiation, cervical carcinoma, hemoglobin level*

RAZINA HEMOGLOBINA U ODGOVORU NA PREOPERATIVNU KEMOIRADIJACIJU U BOLESNICA S LOKALNO UZNAPREDOVALIM RAKOM VRATA MATERNICE

Sažetak

Razina hemoglobina važan je prognostički pokazatelj u odgovoru na zračenje bolesnica s ginekološkim malignomima. Anemija udružena s rakom vrata maternice česta je i pokazatelj je ne samo biološki agresivnijeg tumora već može biti i uzrokom slabijeg odgovora na zračenje. Kemoiradijacija je uobičajeni način liječenja bolesnica s lokalno uznapredovalim

rakom vrata maternice s ciljem poboljšanja odgovora na liječenje i preživljenja. Operativni zahvat nakon neoadjuvantne kemoiradijacije smanjuje lokalni recidiv.

U Zavodu za ginekološku onkologiju u razdoblju od 1/01 do 12/04 liječene su 64 bolesnice s rakom vrata maternice. Stadij bolesti određivao se prema FIGO-klasifikaciji (od Ib1-IIIa), patohistološki se radilo o pločastom i žljezdanom tipu raka vrata maternice, a opće stanje određivalo se prema ECOG-u (0-1). U svih bolesnica provedeno je vanjsko zračenje zdjelice u dozi od 40 Gy, a potom i unutarnje zračenje, 1 aplikacija LDR s Cezijem 137 u dozi od 35-38 Gy u točku A. Tijekom vanjskog zračenja bolesnice su primale 1x tjedno Cisplatinu u dozi od 40 mg/m² ukupno 4x kao radiosenzibilizator. Nakon provedenog zračenja bolesnice su operirane (histerektomija s adneksotomijom uz resekciju forniksa vagine, a u nekih bolesnica učinjena je i zdjelčna limfadenektomija). Za vrijeme zračenja pratili smo vrijednosti hemoglobina 1x tjedno kao i opće stanje koje smo stupnjevali prema ECOG-u.

Sve bolesnice su prije operacije ozračene. Srednja doza u točku A bila je 77,2 Gy, prosječno vrijeme zračenja bilo je 34,37 dana. Vrijeme između završetka zračenja i operacije iznosilo je 34,4 dana. Razina hemoglobina i veličina tumora znatno su se smanjivali tijekom kemoiradijacije. Procjenu odgovora na kemoiradijaciju učinili smo na patohistološkom nalazu uklonjenog vrata maternice prema WHO podjeli kao potpuni odgovor (CR), djelomičan odgovor (PR) te stabilnu bolest (SD). Početna vrijednost hemoglobina te redovito praćenje razine hemoglobina tijekom kemoiradijacije pokazali su kako je veći postotak CR i PR u bolesnica s višim vrijednostima hemoglobina (>120 mg/L nasuprot <100 mg/L).

Bazalne i kontrolne vrijednosti hemoglobina u bolesnica s lokalno uznapredovalim rakom vrata maternice koje su liječene kemoiradijacijom i operacijom pokazale su se kao dobar prognostički pokazatelj odgovora na primijenjeno liječenje. Ovaj pokazatelj mora se uzeti u obzir s ostalim kao što su: stupanj uznapredovalosti bolesti, histološka diferencijacija i opće stanje bolesnice.

KLJUČNE RIJEČI: kemoiradijacija, rak vrata maternice, razina hemoglobina

INTRODUCTION

Nowadays, the incidence of cervical carcinomas is decreasing owing to the preventive tests and vaccine against certain HPV-types for the adolescents. Nevertheless, cervical carcinoma is still one of the most common gynecological cancers and is the third among all cancers that affect women. It appears mostly in young women in the generative age. Locally advanced cervical carcinoma is very common in transition countries that lack good preventive programs. There are two modalities of treatment for patients with locally advanced cervical carcinoma – neoadjuvant chemoradiation followed by surgery or radical chemoradiation.

In the past two decades, there have been no changes in the survival percentage of patients with locally advanced cervical carcinoma. It is obvious that concomitant chemotherapy and radiation lead to the higher survival rates in contrast to the radiation alone. It is believed that there are a number of surgeons who avoid radiation therapy, because the anatomical findings are somehow different. On the other hand, from the literature data, it is obvious that there are no postoperative complications after 4–6 weeks of radiation (1, 2). Apart from the size of the primary tumor, another important prognostic factor is the hemoglobin level before and after chemoradiation (3, 4).

In our Department, for the last 10 years, all the patients with locally advanced cervical carcinoma (FIGO stages Ib1–IIb) underwent chemoradiation followed by radical surgery.

MATERIALS AND METHODS

Sixty-four female patients with locally advanced cervical carcinoma were treated at the Department of Gynecologic Oncology, University Medical Center in Zagreb from January 2001 to December 2004. Our retrospective study included patients with characteristics, such as pathohistologically improved cervical carcinoma (squamous or glandular type), FIGO Ib–IIIa, external radiotherapy on the pelvis with concomitant chemotherapy including cisplatin, brach therapy with Cs 137 (LDR: low-dose rate), and hemoglobin level before and during RT-KT and surgery.

Histological classification was done according to the WHO criteria, and FIGO classification was used to detect the stage of the cancer. The results of RT and KT were classified based on the WHO criteria, such as CR (complete response), PR (partial response), and SD (stabilization of the disease). Furthermore, the general conditions of the patients were determined according to the ECOG performance status.

All the patients were treated using Linear accelerator, Siemens, with two opposite fields on the whole pelvis with 15 MV with 42 Gy and 22–23 fractions (daily TD 1.7–1.9 Gy). During external radiotherapy, 40 mg/m² of cisplatin was administered to patients as a radiosensibilizer, through I-h infusion with adequate hydration. After external radiotherapy, all the patients underwent brach therapy with Cs 137 (LDR), 35–38 Gy at point A. After 2–4 weeks of brach therapy, the surgery was performed (hysterectomy, bilateral ovariectomy, resection of the parametrias and vaginal fornices, and lymph nodes biopsy). Findings on the cervix uteri were divided into CR (complete response – no tumor-like cells), PR (partial response – with tumor cells treated with radiation), and SD (stabilization of the disease – tumor cells treated with radiation and vital tumor cells). Furthermore, the hemoglobin level during chemoradiation was discussed. The basal hemoglobin level was the one before the beginning of the RT. Hemoglobin levels (g/dl) were measured once every week before the application of cisplatin.

RESULTS

We analyzed 64 female patients with locally advanced cervical carcinoma who were treated at the Department of Gynecologic Oncology, University Medical Center in Zagreb from January 2001 to December 2004. The median age of patients was 44 years (29–65 y), 7 patients were in FIGO stage Ib1 (11%), 14 were in FIGO stage Ib2 (22%), 2 were in FIGO stage IIa (3%), 38 were in FIGO stage IIb (60%), and 3 patients were in FIGO stage III (4%). It can be observed that the majority of our patients had locally advanced cervical cancer (with parametrial indurations, Table 1). According to the pathohistological findings, there were two categories: squamous cell carcinomas and glandular cell carcinomas in 49 (77%) and 15 (23%) patients, respectively. The diameter of the primary tumor was measured before the therapy – the median size was 4.5 cm (1–8 cm). The patients' general condition was scaled according to the ECOG performance status: ECOG 0 = 51 patients (80%) and ECOG 1 = 13 (20%) (Table 1). The hemoglobin level was measured at the beginning of chemotherapy and after the treatment. The median hemoglobin level was observed to be 115 g/

Table 1.

PATIENTS' CHARACTERISTICS

PATIENT'S CHARACTERISTICS	NEOADJUVANT CHEMORADIATION AND RADICAL SURGERY
– Number of patients (N)	64
– Age (years)	44 (29 – 65)
– FIGO stage (N, %)	
IB1	7 (11%)
IB2	14 (22%)
IIA	2 (3%)
IIB	38 (60%)
III	3 (4%)
– Histology (N, %)	
Squamous carcinoma	49 (77%)
Glandular carcinoma	15 (23%)
– Tumor diameter (cm)	4.5 (1 – 8)
– ECOG performance status (N, %)	
0	51 (80%)
1	13 (20%)

Table 2.

PATIENTS' CHARACTERISTICS

PATIENT'S CHARACTERISTICS	NEOADJUVANT CHEMORADIATION AND RADICAL SURGERY
– Hemoglobin level (mg/l)	
basal	115 (92 – 139)
after CT-RT	107 (87 – 146)
– Dosage at point A (Gy)	77.23 (44 – 95)
– Duration of CT-RT (days)	34.37 (25 – 55)
– Response on CT-RT (N, %)	
Complete response	22 (34%)
Partial response	38 (60%)
Stable disease	4 (6 %)
– Time interval CT-RT	34.4 (11 – 100)
– OP (days)	
– Overall response	
Complete response	32 (50%)
Partial response	21 (21%)
Stable disease	11 (17%)

dl (92–139 g/dl). After chemotherapy completion, the hemoglobin level was 107 g/dl (87–146 g/dl). Special attention was given to the duration of chemoradiation – the median time was 34.37 days (25–55 days). After the termination of chemotherapy, control gynecological examination was performed and the results were classified as CR (22; 34%), PR (38; 60%), and SD (4; 6%). The time interval between the end of chemotherapy and before the surgery was also evaluated. The median time was 34.4 days (11–100 days).

The final results were established according to the WHO pathohistological criteria on the cervix uteri. In 32 patients (50%), no tumor cells were

found (CR), in 21 patients (21%) there was no vital tumor cells (PR), and in 11 patients (17%) neither the tumor nor vital tumor cells were detected (SD) (Table 2).

We concluded that patients with higher basal hemoglobin levels show better overall results, according to the WHO criteria.

DISCUSSION AND CONCLUSIONS

The first data on the usefulness of concomitant chemoradiotherapy in patients with locally advanced cervical carcinoma were from the 21st century. Later, only radiotherapy was abandoned (5, 6). However, investigations showed that concomitant chemoradiotherapy demonstrates significantly better results based on the quality of life of the cured patients (almost 30–50% better). Nevertheless, the biggest problem still is the recidivism of the illness in the area treated by radiation. This problem is particularly challenging in patients with lower basal hemoglobin levels (almost 80% more recidivism was observed in patients with the basal hemoglobin level <10 g/dl). However, transfusion and erythropoietin administered during RT-KT led to better oxygenation of the tumor, and consequently, ensured better sensitivity to RT (7-9).

Owing to the high percentage of the post-chemoradiotherapy recidivism, surgery was performed after RT-KT. Nevertheless, the results of such combined therapy are controversial, and no randomized study showed better recoveries after such treatment and the morbidity was also high (10). However, there were some non-randomized trials that demonstrated the usefulness of such therapy for the residual tumor of ≤ 2 cm in size, mostly with respect to disease-free interval and long life. Locally, recidivism is the main cause of unsuccessful therapy (11). Moreover, recidivism can locally cause chronic pain and poor quality of life. Hence, surgery after RT-KT is an important step in the therapy.

As it can be observed, 50, 21, and 17% of our patients presented CR, PR, and SD, respectively. In our opinion, patients with PR and SD outcomes are candidates for surgery.

The implications of hemoglobin level on PR are known for a long time. However, in many analyses, it was not possible to prove the signifi-

cance of hemoglobin level during RT-KT as well as owing to the poor outcome. It is believed that the clinical impact of anemia on the tumor is due to the aggressiveness of the tumor. Our results revealed that patients with a higher basal hemoglobin level had better overall results (12).

CONCLUSION

It can be concluded that primary chemoradiation therapy followed by (radical) surgery is an effective treatment approach in patients with locally advanced cervical carcinoma. However, further investigations are necessary to determine whether such an approach leads to better recoveries and better implications on the quality of life.

REFERENCES

1. Kornovsky Y, Gorchev G. Hystopathological findings in postoperative specimens in cervical cancer patients with stage Ib2-IVa after neoadjuvant chemotherapy and preoperative plus postoperative radiotherapy. *J Buon* 2007; 12(1): 57-63
2. Houvenaeghel G, Lelievre L, Buttarelli M, Jacquemier J, Cardopino X, Viens P, Gonzague-Casabianca L. Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol* 2007; 33(4): 498-503
3. Ferrandina G, Distefano M, Smaniotta D, Morganti A, Paglia A, Macchia G, Corvari B, Lorusso D, Scambia G. Anemia in patients with locally advanced cervical carcinoma administered preoperative radiochemotherapy: association with pathological response to treatment and clinical outcome. *Gynecol Oncol* 2006; 103(2): 500-5
4. Fuso L, Mazzola S, Marocco F, Ferrero A, Domp   D, Carus Ap, Zola P. Pretreatment serum hemoglobin level as a predictive factor of response to neoadjuvant chemotherapy in patients with locally advanced squamous cervical carcinoma: a preliminary report. *Gynecol Oncol* 2005; 99(3 suppl 1): S187-91
5. Houvenaeghel G, Lelievre L, Rigouard L, Buttarelli M, Jacquemier J, Viens P, Gonzague-Casabianca L. Residual pelvic lymph node involvement after concomitant chemoradiation for locally advanced cervical cancer. *Gynecol Oncol* 2006; 102(1): 74-9
6. Houvenaeghel G, Lelievre L, Gonzague-Casabianca L, Buttarelli M, Moutardier V, Goncalves A, Resbeut M. Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol* 2006; 100(2): 338-43
7. Papanikolaou A, Kalogiannidis I, Misailidou D, Goutzioulis M, Stamatopoulos P, Makedos A, Vatopoulou

- A, Makedos G. Results on the treatment of uterine cervix cancer: ten years experience. *Eur J Gynaecol Oncol* 2006; 27(6): 607-10
8. Mariagrazia D, Anna F, Gabriella F, Francesco F, Daniela S, Giuseppe D, Alessio M, Giovanni S. Preoperative chemoradiotherapy in locally advanced cervical cancer: long-term outcome and complications. *Gynecol Oncol* 2005; 99(3 suppl 1): S166-70
 9. Shibata K, Kikkawa F, Suzuki Y, Terauchi M, Kajiyama H, Ino K, Mizutani S. Usefulness of preoperative chemoradiation in locally advanced cervical carcinoma. *Gynecol Obstet Invest* 2004; 57(2): 93-9
 10. Winter We, Maxwell Gl, Tian C, Sobel E, Rose Gs, Thomas G, Carlson Jw. Association of hemoglobin level with survival in cervical carcinoma patients treated with concurrent cisplatin and radiotherapy: a gynecologic oncology group study. *Gynecol Oncol* 2004; 94(2): 495-501
 11. Chen Ca, Cheng Wf, Wei Lh, Su Yn, Hsieh Cy. Radical hysterectomy alone or combined with neoadjuvant chemotherapy in the treatment of early stage bulky cervical carcinoma. *J Formos Med Assoc* 2002; 101(3): 195- 202
 12. Obermair A, Cheuk R, Horwood K, Janda M, Bachiary B, Schwanzelberger B, Stoiber A, Nicklin JI, Perrin Lc, Crandon Aj. Impact of hemoglobin levels before and during concurrent chemoradiotherapy on the response of treatment in patients with cervical carcinoma: preliminary results. *Cancer* 2001; 92(4): 903-8

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