Journal of BUON **14:** 197-202, 2009

ORIGINAL ARTICLE

Evaluation of the possible benefits of post-radiotherapy surgery after concomitant chemoradiotherapy with a new radio-sensitizing regimen (irinotecan / CPT-11, interferon A2b and amifostine) for advanced-stage cervical carcinoma. Preliminary results of a pilot phase-II study

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Summary

Purpose: *This phase II pilot study was conducted to evaluate the results of a three-modality approach (which included post-chemoradiotherapy surgery) in advanced-stage cervical carcinomas.*

Patients and methods: *Thirty-six patients underwent either surgery or were put on follow-up after having received radical cervical radiotherapy (RT) combined with radio-sensitizing chemoimmunotherapy with irinotecan (CPT-11), interferon (IFN) A2b, and amifostine. The last selection (surgery or follow-up) was based on clinical evaluation (downstaged or not). Feasibility, morbidity, surgical outcome and survival were evaluated.*

Results: *Twenty-six patients had stage IIb and 10 IIIb disease at diagnosis. Sixteen (44%) were clinically downstaged, thus becoming eligible for surgery. Twelve (33%) were operated and the others were put on follow-up. There was no significant increase in treatment-related morbidity of the group of patients receiving three-modality therapy, since only one intraoperative complication had occurred. In 58% of the operated patients, chemoradiotherapy-resistant tumor was found on pathology of the cervical specimens, while 29% of them had lymph nodes infiltrated by the tumor. After a median follow-up of 42.5 months, overall survival (OS) of operated vs. non-operated patients (88 vs. 56%, respectively) show only a trend toward significance (p=0.10). The overall recurrence/metastasis rate was 36.1% and the disease-free survival (DFS) 56% for operated vs. 76% for non-operated patients, respectively (p=0.63).*

Conclusion: *These results indicate that post-chemoradiotherapy surgery is justified because of the high rate of residual disease found. Morbidity can be effectively limited with proper patient selection. A considerable survival benefit is expected, although this remains to be confirmed with phase III studies.*

Key words: advanced stage cervical carcinoma, amifostine, chemoradiotherapy, interferon, irinotecan, post-radiotherapy surgery

Introduction

Advanced-stage cervical carcinomas have been traditionally treated with external beam RT plus intracavitary brachytherapy. Over the last 8 years, solid evidence has been reported indicating that the concomitant use of chemotherapy and RT produces better results in terms of DFS and OS compared to RT alone, and has thus become the gold standard [1-8].

Nevertheless, these results are still unsatisfactory since the OS rate for advanced carcinomas is approximately 53% [9]. So far, it appears that there are two issues of scientific interest in the effort to improve the above figures. The first is the use of different and po-

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Received 29-08-2008; Accepted 28-09-2008

tentially more effective radiosensitizing agents, alone or in combination, in various schedules and doses. At present, single-agent therapy with cisplatin seems to be the standard choice [6,10]. The second issue is the three-modality approach, which includes surgery after chemoradiation.

In 2002, we initiated a phase I feasibility study of external RT supplemented by intracavitary radiation in combination with concurrent weekly irinotecan+IFN A2b and amifostine as a cytoprotective agent.

There were 3 evaluation points of this protocol. The first one was to see the effectiveness of this three-agent regimen in terms of survival, but also to evaluate its tolerability. The second was to see if this chemoradiation protocol produced a considerable number of downstaged patients in whom surgery could be offered, thus ending in a three-modality approach. And finally, the third was to evaluate the possible benefit of surgery on DFS and OS given the shortcomings of a non-randomized trial.

The promising results of the three-agent chemoradiotherapy, regarding its effectiveness and tolerability were presented in a preliminary report [11]. In the present study, we report the preliminary (short-term) results regarding the possible benefits of post-RT surgery on DFS and OS.

Patients and methods

In 2002, the scientific review board of "Metaxa" Cancer hospital approved a treatment protocol for advanced-stage cervical carcinomas with concomitant use of RT and 3 agents, 2 radiosensitizing ones (irinotecan and IFN A2b), and the cytoprotective amifostine (ethyol).

From November 2002 until April 2005, 36 patients entered the study and completed the treatment protocol. Informed consent was taken in all cases. A minimum of 6 months follow-up time was required for inclusion in the present analysis.

Chemoradiotherapy and patient grouping

Standard fractionated external beam RT using 6 MeV linear accelerator (180 cGy/day) for 5 days every week up to a total dose of 5400 cGy was delivered, followed by intracavitary application of cesium (Cs), for a total tumor dose of 2000 cGy. Concomitantly, irinotecan (30 mg/m^2) was given i.v. on day 1 of each RT week, interferon A2b (3 MIU) twice weekly s.c., while amifostine (500 mg) was given i.v. one hour prior to each RT fraction [11]. Following the completion of the above chemoradiation schedule, all patients were evaluated for response by a new CT or MRI scan and clinical examination. Those who had achieved clinical disease downstaging to a stage that was considered operable according to standard FIGO guidelines (≤ IIa) were offered the opportunity of surgery. All other patients were followed-up.

These 36 patients formed our study population and were all evaluated after the completion of their chemoradiation for possible surgical intervention. Table 1 summarizes the patient characteristics. Our purpose was to form and compare 3 subgroups of patients: a) patients in whom clinical downstaging had been achieved and who underwent hysterectomy (group A); b) patients in whom clinical downstaging had been achieved but refused operation (group B); and c) patients in whom downstaging had not been achieved (group C).

Surgery was carried out 6 weeks after the completion of chemoradiation. We sought to determine possible differences in DFS and OS among the 3 subgroups, identify the complication rate when the three-modality approach was used, and determine the percentage of operated patients with positive histological findings, a number that would directly justify (or not) the addition of surgery after chemoradiation.

Statistical considerations

Statistical analysis was performed using SPSS 12 software for Windows. OS and DFS were computed using the Kaplan-Meier method, while the statistical differences were estimated by the log-rank test. Other

Table 1. Patient characteristics

Characteristic	*No. of patients*	*%*
No. of patients	36	100.0
Mean age, years (range)	48 (32-80)	
FIGO stage		
IIb	26	72.2
IIIb	10	27.8
Histology		
SCC	32	88.9
Adeno-SCC	4	11.1
Grade		
1	3	8.3
2	16	44.5
3	12	33.3
2 - 3	5	13.9
LVSI		
Yes	3	8.3
No	33	91.7

SCC: squamous cell carcinoma, LVSI: lymphovascular space involvement

estimations were performed by the Fisher's exact test and p-value ≤ 0.05 was used as level of statistical significance.

Results

The patient mean follow-up time was 42.5 months (95% confidence interval/CI 27-58). Of the 36 patients, 20 (55.6%) were not downstaged at the end of their chemoradiation and were followed-up (group C), 12 (33.3%) were downstaged and underwent surgery (group A), and the remaining 4 (11.1%) were downstaged but refused surgical intervention (group B).

Due to the limited number of patients in group B, which would limit the statistical power of comparisons, in the present preliminary report, we merged the above 4 patients with the non-downstaged, non-operated ones (group C), in order to proceed with our statistical analysis and comparisons.

Regarding the surgical procedure, 6/12 patients underwent type III radical hysterectomy and pelvic lymphadenectomy, 5/12 type I-II radical hysterectomy without lymphadenectomy, and 1/12 underwent total exenteration and pelvic lymphadenectomy. None of the patients underwent paraaortic lymphadenectomy but we relied on the preoperative CT or MRI scan and the intraoperative palpation of the retroperitoneum which were negative for paraaortic lymph node involvement in all cases.

Only one case with an intraoperative complication was recorded (wide perforation of the bladder which was repaired in time) and none postoperatively.

The histological findings with respect to the operation performed are shown in Table 2. The important findings are that in 7/12 (58%) operated patients, residual disease was discovered in the cervix, 2/12 (17%) had parametrial involvement and 2/7 (29%) of them had also infiltrated lymph nodes.

In Table 3 the sites of recurrences/metastases are presented. So far, 13 events have occurred: 4 (33.33%) among operated and 9 (37.5%) among non-operated patients (p=0.008). From these 13 (36.1%) patients who developed such events, 9/13 had distant metastases to different sites (3 operated and 6 followed-up), while the remaining had local recurrence.

The median overall time to recurrence and/or metastasis was 16 months (range 5-31). It is noteworthy that local recurrences/metastases occurred in a significantly shorter time interval after the completion of chemoradiation in patients who were followed-up, compared to those who underwent post-chemoradiotherapy hysterectomy (median 11.75 vs. 20.25 months, p <0.05).

Table 3. Sites of metastases / recurrences

Site	*Operated patients (n=12) n (%)*	*Followed-up patients (n=24) n (%)*
Local central recurrence	–	2 (8.3)
Local lateral recurrence	1 (8.3)	1 (4.2)
Local central + paraaortic LN	–	1 (4.2)
Lungs	2 (16.7)	1 (4.2)
Liver + lungs	1 (8.3)	1 (4.2)
Liver + paraaortic LN	–	2 (8.3)
Bones	–	1 (4.2)
No recurrence / metastasis	8 (66.7)	15 (62.4)

LN: lymph nodes

Table 2. Histological findings of the operated patients (n= 12)

	Type III RH + PL	*Type I-II RH*	*Exenteration + PL*	*Total n (%)*
No. of patients	6	5	1	
Cervix				
+	4	2	1	7 (58)
–	2	3	0	5 (42)
Lymph nodes				
+	1		1	2 (29)
–	5		0	5 (71)
Parametrium				
+	1	0	1	2 (17)
–	5	5	0	10 (83)
Other pelvic organs				
+			1	1 (8)
–			0	0

RH: radical hysterectomy, PL: pelvic lymphadenectomy

Table 4. Overall survival of 36 patients with respect to the treatment group

	Operated patients n (%)	*Followed-up patients n (%)*
Died of disease	1 (8.3)	5 (20.8)
Died of other causes	0	2 (8.4)
Alive with disease	3 (25.0)	4 (16.6)
Alive with no evidence of disease	8 (66.7)	13 (54.2)
Total	12 (100)	24 (100)

Table 4 presents the current status of the patients with respect to the treatment they had undergone. So far 6 patients have died from their disease, 5 from the follow-up group and 1 from the operated group, while 2 from the patients followed have died from unrelated causes.

The 5-year actuarial OS of the 2 patient groups (operated vs. non-operated) is 88% and 56%, respectively, but despite this 32% survival difference, the statistical comparison shows a modest-only trend toward significance (p=0.10; Figure 1). However, the fact that there was only one death in the operated group limits the statistical power of this comparison with the log-rank test.

Moreover, the 5-year DFS was 58% and 76% for non-operated and operated patients, respectively (Figure 2), yielding a non-significant difference (p=0.63).

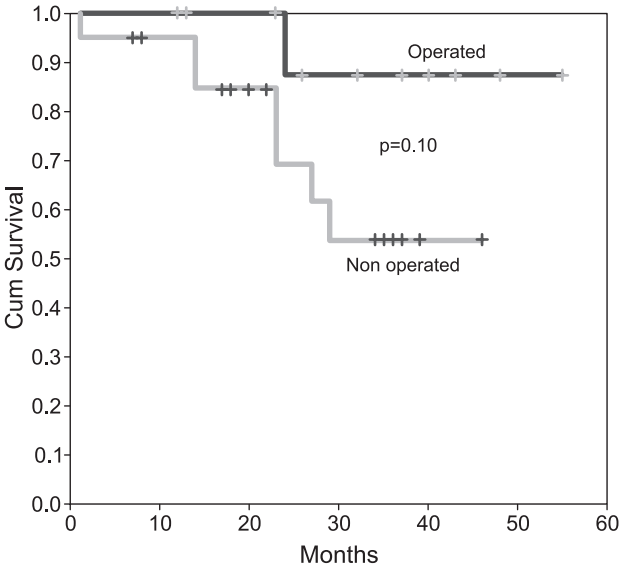

Figure 1. Overall survival of operated and non operated patients.

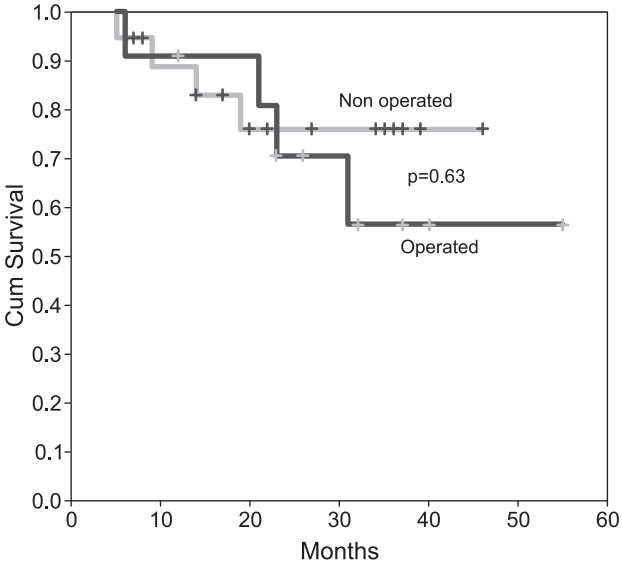

Figure 2. Disease-free survival of operated and non operated patients.

Discussion

The current phase II study presents the results of the application of a new three-agent chemoradiation regimen, followed–where appropriate–by surgery in advanced cervical carcinomas (stages IIb–IIIb), thus allowing a multidisciplinary three-modality treatment.

As it has been previously reported, both irinotecan [12,13] and IFN A2b [12,14] are effective radiosensitizing and chemotherapeutic agents in patients with cervical cancer. On the other hand, amifostine, a cytoprotective agent, has been found to ameliorate grade III-IV chemoradiotherapeutic toxicities [15,16].

With the above chemoradiation protocol, we achieved a clinical complete response – which in the present evaluation is defined as clinical downstaging in terms of parametrial disease – in 44.4% of the patients, thus rendering them eligible for surgery. Moreover, the chemotherapy regimen of irinotecan+IFN A2b does not represent a standard treatment, and it is not known how it compares to cisplatin or cisplatin/5-FU in terms of its radiosensitizing potential, as well as its efficacy in locally advanced cervical carcinoma in a formal randomized phase II/III study. However, in experimental/preclinical studies [12-14] and in a prior phase I study of our group [11], the irinotecan+IFN A2b+amifostine combination has demonstrated high efficacy that compares favorably to standard cisplatin or cisplatin/5-FU chemotherapy regimens.

Regarding the three-modality approach, one of the major concerns that should be stressed out is

the incidence of short- and long-term postoperative complications. In the present study this factor was of minor importance, since only one intraoperative and none postoperative complications occurred. This fact is important because underlines that when proper patient selection is performed, the three-modality approach is not only feasible but also safe. One possible explanation is that we selected for surgery only those patients who were clinically and radiologically downstaged, in contrast to what has been traditionally described in the majority of other published studies [17-19].

The primary goal of the operation was to remove the uterus in order to eradicate centrally located disease, which represents an imminent site of failure, as well as render eligible patients free of residual disease, ultimately aiming to improve DFS and OS. Nevertheless, the selection of the type of the operation was made by the attending surgeon intraoperatively.

The pathological evaluation of the surgical specimens revealed chemoradiotherapy resistant residual disease of the cervix in 58% of the operated patients, 17% parametrial invasion, and 29% lymph node metastasis for patients in whom lymphadenectomy had been performed. Apparently, residual disease figures are similar to those reported by other authors, advocating in favor of the addition of surgery (three-modality treatment) in order to improve survival [17-21]. The addition of surgery was done on a selected basis, i.e. to those patients who demonstrated significant downstaging, and there has been no control for this intervention, such as a group of patients achieving downstaging and being randomized to observation (no surgery). However, as highlighted earlier, this was a pilot phase II study, and as such the aim was to demonstrate feasibility and efficacy in this setting. Therefore, future randomized studies will likely address the contribution of surgery to patients that will be clinically and /or radiologically downstaged.

So far, the overall incidence of metastases/recurrences has been 22.2%, a figure which is comparable with the 28.6% failure rate (both distant and locoregional) reported by Houvenaeghel et al. [18], and the 17.9% reported by Mariagrazia et al. [17]. It is noteworthy that local recurrences took place in only 8.3% of the operated patients compared with 16.7% (including 4.2% with both local and distant metastasis) of the non-operated patients ($p < 0.001$). Therefore, it seems that local control was considerably improved in the present study with the three-modality approach. The median time to relapse has been 16 months (range 5-31).

These preliminary results show a possible survival advantage when the three-modality approach is used, without significant morbidity or mortality. The relative small number of patients in each treatment subgroup and especially the even smaller number of deaths in the OS analysis appears to be the logical explanation of the inability to detect statistically significant differences ($p=0.10$). On the other hand, the recurrence/metastasis rate appears to be comparable ($p=0.63$) between operated vs. non-operated patients, whereas a time to relapse benefit may be present for the operated patients. This last assumption needs to be verified with the addition of more patients and longer follow-up. However, it is important to emphasize that any comparisons in DFS, time to treatment failure and OS, made on the basis of downstaging and subsequent surgery after chemoradiotherapy may be flawed by patient selection and more adverse disease-presenting features in patients not being surgical candidates vs. those becoming eligible for operation. One could therefore argue that treatment might be selecting a subgroup of patients with more favorable disease characteristics at presentation that were eventually going to demonstrate improved responses and operability. That is to say that the present study was a single-arm non-randomized phase II study, with its anticipated principal end-point being feasibility and efficacy, and was not designed to detect differences in outcome between operated vs. non-operated patients. The suggested possible benefit of post-chemoradiotherapy surgery can only be addressed in future prospectively designed phase III randomized studies evaluating the role of surgery in patients that are clinically/radiologically downstaged after an effective chemoradiation schedule as the one applied in the current study.

In conclusion, the current phase II study has shown that combined chemoradiation with a novel 3-drug regimen of irinotecan, IFN A2b and amifostine, is adequately active and safe in locally advanced inoperable cervical cancer (stage IIb-IIIb), thus warranting randomized phase II-III comparisons to the more standard cisplatin-based chemoradiation schedules. The considerably high rates of downstaging and operability lend credence to the design of adequately powered prospective phase III studies evaluating the role of surgery in patients rendered surgical candidates.

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